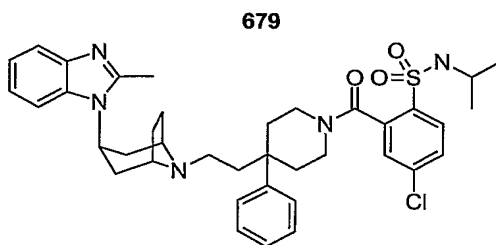
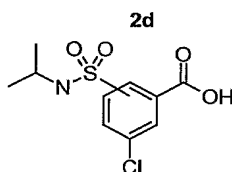


Example 679

4-Chloro-N-isopropyl-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



A mixture of 5-chloro-2-[(isopropylamino) sulfonyl]benzoic acid and 3-chloro-4-[(isopropyl amino)sulfonyl]benzoic acid, 2d.



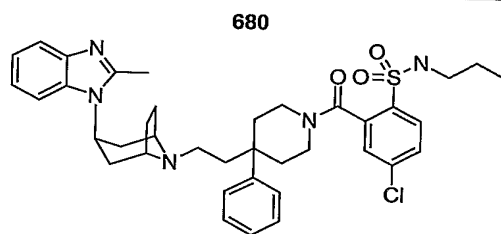
The mixture was prepared from a mixture of 3-chloro-4-(chlorosulfonyl)benzoic acid and 5-chloro-2-(chloro sulfonyl)benzoic acid 2a and isopropyl amine following the general procedure for 5-chloro-2-[(methylamino) sulfonyl]benzoic acid and 3-chloro-4-[(methylamino) sulfonyl]benzoic acid 2b. The crude reaction mixture was carried on without further purification. ES-LCMS m/z 276 (M-H).

4-Chloro-N-isopropyl-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide (example 679). The title compound was prepared from a mixture of 5-chloro-2-[(isopropylamino) sulfonyl]benzoic acid and 3-chloro-4-[(isopropyl amino)sulfonyl]benzoic acid 2d and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1] oct-3-yl}-1H-benzimidazole dihydrochloride II following the general procedure for tert-butyl {2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl} sulfonylcarbamate 1c. The desired regioisomer was purified by column chromatography on silica gel eluting with 10% methanol in ethyl acetate to afford 4-chloro-N-isopropyl-2-[(4-{2-[3-(2-

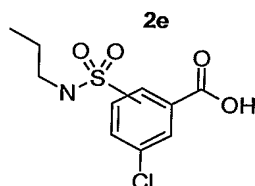
methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-phenyl piperidin-1-yl)carbonyl] benzenesulfonamide 4 as a white solid (30 mg, 22% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, 1H, J=8.0Hz), 7.65 (d, 1H, J=7.3Hz), 7.52 (m, 1H), 7.40–7.11 (m, 9H), 4.99 (d, 1H, J=7.32 Hz), 4.60 (m, 1H), 4.20 (m, 1H), 3.49–3.22 (m, 6H), 2.56 (s, 3H), 2.40–2.32 (m, 3H), 2.18 (m, 1H), 1.98–1.66 (m, 1H), 1.62 (m, 2H), 1.10 (d, 6 H, J=6.59Hz). ES-LCMS m/z 690.45 (M+2H). Analytical HPLC (Method Y) Rt 5.03 (88.43%).

Example 680

4-Chloro-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-N-propylbenzenesulfonamide



A mixture of 5-chloro-2-[(propylamino) sulfonyl]benzoic acid and 3-chloro-4-[(propylamino) sulfonyl]benzoic acid, 2e.



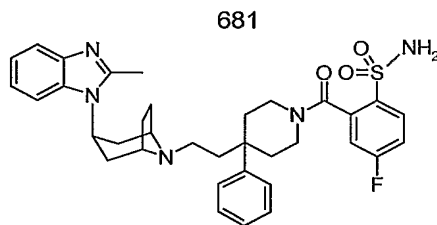
The mixture was prepared from a mixture of 3-chloro-4-(chlorosulfonyl)benzoic acid and 5-chloro-2-(chloro sulfonyl)benzoic acid 2a and propyl amine following the general procedure for 5-chloro-2-[(methylamino) sulfonyl]benzoic acid and 3-chloro-4-[(methylamino) sulfonyl]benzoic acid 2b. The crude reaction mixture was carried on without further purification. ES-LCMS m/z 276 (M-H).

4-Chloro-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-N-propylbenzene sulfonamide (example 680). The title compound was prepared from a mixture of 5-chloro-2-[(propylamino) sulfonyl]benzoic acid and 3-

chloro-4-[(propylamino) sulfonyl]benzoic acid 2e and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride II following the general procedure for tert-butyl {2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl} sulfonylcarbamate 1c. The desired regioisomer was purified by column chromatography on silica gel eluting with 10% methanol in ethyl acetate to afford 4-chloro-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-aza bicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-N-propylbenzenesulfonamide 5 as a white solid (15 mg, 11% yield). ¹H NMR (400 MHz, CDCl₃) δ (8.12, 1H, J=8.0Hz), 7.65 (m, 1H), 7.52 (m, 1H), 7.41–7.12 (m, 9H), 5.10 (t, 1H, J=6.0Hz), 4.59 (m, 1H), 4.20 (m, 1H), 3.48–3.19 (m, 6H), 2.89 (q, 1H, J=6.6Hz), 2.56 (s, 3H), 2.55–2.32 (m, 3H), 2.17 (m, 1H), 1.93–1.64 (m, 10H), 1.61 (m, 1H), 1.50 (m, 2H), 0.882 (t, 3H, J=7.3Hz). ES-LCMS m/z 690.33 (M+2H). Analytical HPLC (Method Y) Rt 5.39 (93.34%).

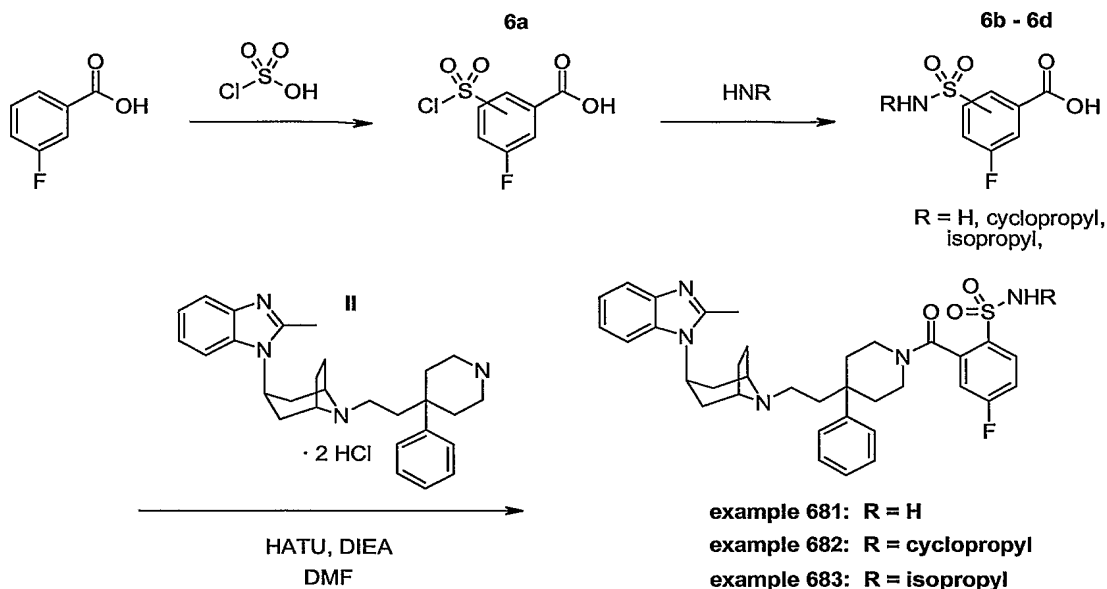
Example 681

4-Fluoro-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide



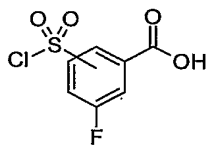
Example 681 was prepared as outlined below.

442



A mixture of 2-(chlorosulfonyl)-5-fluorobenzoic acid and 4-(chlorosulfonyl)-3-fluorobenzoic acid, 6a.

6a

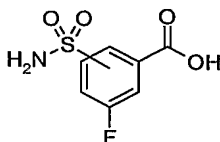


- 5 3-Fluorobenzoic acid (7.0 g, 50 mmol, 1 equiv) was added at 0 °C to chlorosulfonic acid (40 mL). The reaction mixture was heated to 130 °C for 6 h, cooled to RT and poured slowly over ice. The product was extracted into diethyl ether, dried and concentrated to provide a 4:1 mixture of regioisomers, 2-(chloro sulfonyl)-5-fluorobenzoic acid and 4-(chlorosulfonyl)-3-fluorobenzoic
- 10 acid 6b, as a brown solid (5.26 g, 46% yield). ¹H NMR (400 MHz, CDCl₃) δ.8.14 (ddd, 1H, J=8.0Hz, 2.4Hz, 1.3Hz), 8.05–8.01 (m, 2H), 7.98 (ddd, 1H, J=6.8Hz, 2.4Hz, 1.6Hz), 7.79 (dd, 1H, J=6.8, 2.4Hz), 7.71 (td, 1H, J=8.1, 2.4Hz). ES-LCMS m/z 237.13 (M-H) for C₇H₅FO₅S.

- A mixture of 2-(aminosulfonyl)-5-fluoro benzoic acid and 4-(aminosulfonyl)-3-fluorobenzoic acid, 6b.*
- 15

443

6b



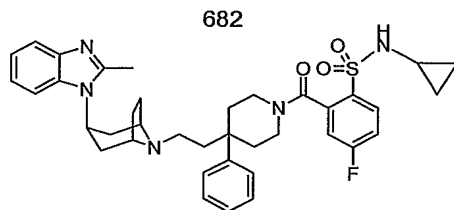
Liquid ammonia was condensed at -78°C into a reaction vessel containing a mixture of 2-(chlorosulfonyl)-5-fluorobenzoic acid and 4-(chlorosulfonyl)-3-fluorobenzoic acid 6a (100 mg, 0.419 mmol, 1 eq.). The reaction mixture was allowed to evaporate slowly upon warming to RT over 18 h. The crude residue contained a mixture of 2-(aminosulfonyl)-5-fluorobenzoic acid and 4-(aminosulfonyl)-3-fluorobenzoic acid and was used without further purification. ES-LCMS m/z 218 (M-H).

4-Fluoro-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide (example 681). The title compound was prepared from a mixture of 2-(aminosulfonyl)-5-fluorobenzoic acid and 4-(aminosulfonyl)-3-fluorobenzoic acid 6b and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-aza bicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydro-chloride II following the general procedure for tert-butyl {2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}sulfonylcarbamate 1c. The desired regioisomer was purified by column chromatography on silica gel eluting with 20% methanol in ethyl acetate to afford 4-fluoro-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide 6 as a white solid (9.8 mg, 20% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.90 (t, 1H, $J=7.7\text{Hz}$), 7.64 (m, 1H), 7.39 (m, 2H), 7.30–7.12 (m, 8H), 5.69 (broad s, 2H), 4.59 (m, 1H), 4.20 (m, 1H), 3.48–3.19 (m, 5H), 2.52 (s, 3H), 2.40–2.32 (m, 3H), 2.18 (m, 1H), 2.04–1.70 (m, 10H), 1.62 (m, 2H). ES-LCMS m/z 630.19 (M+H). Analytical HPLC (Method Y) R_t 4.16 (90.0%).

Example 682

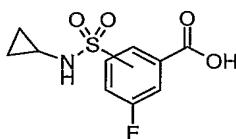
N-Cyclopropyl-4-fluoro-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzene sulfonamide was synthesized analogously to example 861.

5



A mixture of 2-[(cyclopropylamino)sulfonyl]-5-fluorobenzoic acid and 4-[(cyclopropylamino) sulfonyl]-3-fluorobenzoic acid, 6c.

6c



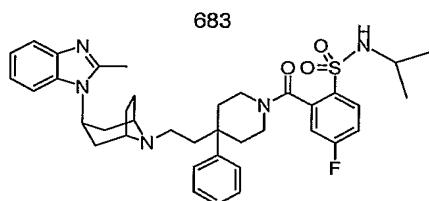
10 The mixture was prepared from a mixture of 2-(chloro sulfonyl)-5-fluorobenzoic acid and 4-(chlorosulfonyl)-3-fluorobenzoic acid 6a and cyclopropyl amine following the general procedure for 5-chloro-2-[(methylamino) sulfonyl]benzoic acid and 3-chloro-4-[(methylamino) sulfonyl]benzoic acid 2b. The crude reaction mixture was carried on without
15 further purification. ES-LCMS m/z 258 (M-H).

The title compound in example 682 was prepared from a mixture of 2-[(cyclopropylamino) sulfonyl]-5-fluorobenzoic acid and 4-[(cyclopropyl amino)sulfonyl]-3-fluorobenzoic acid 6c and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole
20 dihydrochloride II following the general procedure for tert-butyl {2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl piperidin-1-yl)carbonyl]phenyl}sulfonylcarbamate 1c. The desired regioisomer was purified by column chromatography on silica gel eluting with 10% methanol in ethyl acetate to afford N-cyclopropyl-4-fluoro-2-[(4-{2-[3-(2-
25 methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-

phenylpiperidin-1-yl)carbonyl]benzenesulfonamide 7 as a white solid (40 mg, 20% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.97 (t, 1H, J=7.4Hz), 7.65 (m, 1H), 7.38 (m, 2H, 7.29–7.12 (m, 8H), 5.87 (s, 1H), 4.59 (m, 1H), 4.19 (m, 2H), 3.50–3.10 (m, 5H), 2.55 (s, 3H), 2.39–2.16 (m, 5H), 1.92–1.73 (m, 10 H), 1.60 (m, 2H), 0.70–0.50 (m, 4H). ES-LCMS m/z 670.18 (M+H). Analytical HPLC (Method Y) Rt 4.35 (94.82%).

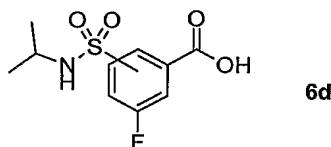
Example 683

4-Fluoro-N-isopropyl-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-
azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-
yl)carbonyl]benzenesulfonamide



Example 683 was prepared analogously to example 681.

A mixture of 5-fluoro-2-[(isopropylamino)sulfonyl]benzoic acid and 4-fluoro-3-[(isopropylamino)sulfonyl]benzoic acid, 6d.



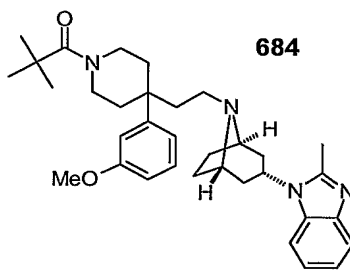
The mixture was prepared from a mixture of 2-(chloro sulfonyl)-5-fluorobenzoic acid and 4-(chlorosulfonyl)-3-fluorobenzoic acid 6a and isopropyl amine following the general procedure for 5-chloro-2-[(methylamino)sulfonyl]benzoic acid and 3-chloro-4-[(methylamino)sulfonyl]benzoic acid 2b. The crude reaction mixture was carried on without further purification. ES-LCMS m/z 260 (M-H).

Title compound in example 683 was prepared from a mixture of 5-fluoro-2-[(isopropylamino)sulfonyl] benzoic acid and 4-fluoro-3-[(isopropylamino)sulfonyl] benzoic acid 6d and endo 2-methyl-1-{8-[2-(4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole

dihydrochloride II following the general procedure for tert-butyl {2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}sulfonyl carbamate 1c. The desired regioisomer was purified by column chromatography on silica gel eluting with
5 10% methanol in ethyl acetate to afford 4-fluoro-N-isopropyl-2-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzenesulfonamide 8 as a white solid (45 mg, 25% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.92 (t, 1 H, J=7.5Hz), 7.65 (m, 1H), 7.38 (m, 2H), 7.29–7.11 (m, 8H), 5.14 (d, 1H, J=7.5Hz), 4.59 (m, 1H), 4.18 (m,
10 1H), 3.54–3.18 (m, 6H), 2.55 (s, 3H), 2.39–2.18 (m, 4H), 1.91–1.81 (m, 10H), 1.61 (m, 2H), 1.15 (m, 6 H). ES-LCMS m/z 672.22 (M+H). Analytical HPLC (Method Y) Rt 4.30 (100.0%).

Example 684

15 1-(((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(3-methoxyphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

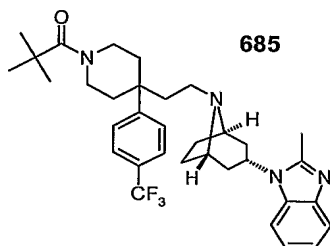


This compound was prepared from 3-methoxyphenylmagnesium
20 bromide and 16a employing methods similar to those described in example 16. ¹H NMR (400 MHz, DMSO-d₆) δ 7.47 (d, 1H, J=7 Hz), 7.34 (d, 1H, J=8 Hz), 7.27 (t, 1H, J=8 Hz), 7.11 (t, 1H, J=7 Hz), 7.08 (t, 1H, J=7 Hz), 6.94 (d, 1H, J=8 Hz), 6.88 (s, 1H), 6.79 (d, 1H, J=8 Hz), 4.51 (m, 1H), 3.75 (m, 2H), 3.74 (s, 3H), 3.23 (m, 4H), 2.50 (s, 3H, obscured by solvent peak), 2.34 (br
25 dd, 2H, J=22, 9 Hz), 2.02 (m, 2H), 1.85 (m, 4H), 1.75 (m, 6H), 1.58 (d, 2H, J=8 Hz), 1.16 (s, 9H). HRMS C₃₄H₄₆N₄O₂ m/z 547.3186 (M+H)_{Cal.}, 543.3699 (M+H)_{Obs.} 543.3708.

447

Example 685

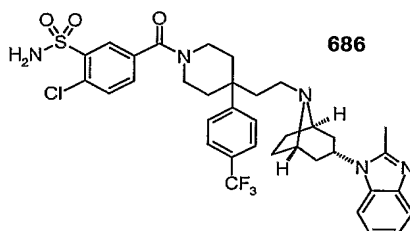
1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(4-
trifluoromethylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-
methyl-1H-benzimidazole



This compound was prepared from 4-trifluoro methylphenylmagnesium bromide and 16a employing methods similar to those described in example 16. ¹H NMR (400 MHz, DMSO-d₆) δ 7.70 (d, 2H, J=8 Hz), 7.62 (d, 2H, J=8 Hz), 7.47 (d, 1H, J=7 Hz), 7.34 (d, 1H, J=7 Hz), 7.10 (t, 1H, J=7 Hz), 7.07 (t, 1H, J=7 Hz), 4.49 (m, 1H), 3.76 (m, 2H), 3.23 (m, 4H), 2.50 (s, 3H, obscured by solvent peak), 2.34 (br. dd, 2H, J=22, 9 Hz), 2.07 (m, 2H), 1.90-1.70 (m, 10H), 1.57 (d, 2H, J=7 Hz), 1.16 (s, 9H). HRMS C₃₄H₄₃F₃N₄O *m/z* 581.3467 (M+H)_{Cal.}, 581.3474 (M+H)_{Obs.}

Example 686

2-Chloro-5-({4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-
azabicyclo[3.2.1]oct-8-yl]ethyl}-4-[4-(trifluoromethyl)phenyl]piperidin-1-
yl)carbonyl)benzene sulfonamide



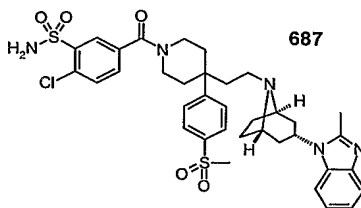
This compound was prepared from 4-trifluoro-methylphenylmagnesium bromide and 16a employing methods similar to those described in example 16. ¹H NMR (400 MHz, CD₃OD) δ 7.95-7.78 (m, 2H), 7.71 (d, 2H, J=8Hz), 7.67 (m, 1H), 7.64 (d, 2H, J=8Hz), 7.52 (br.d, 1H, J=7 Hz), 7.42 (br. d, 1H,

J=7 Hz), 7.20 (t, 1H, J=7 Hz), 7.17 (t, 1H, J=7 Hz), 4.74 (m, 1H), 4.19 (m, 1H), 3.40 (m, 4H), 3.18 (m, 1H), 2.52 (s, 3H), 2.43 (m, 3H), 2.25 (m, 1H), 1.99 (m, 10H), 1.71 (d, 2H, J=7 Hz). HRMS $C_{36}H_{39}ClF_3N_5O_3S$ m/z 714.2492 (M+H)_{Cal.}, 714.2492 (M+H)_{Obs.}

5

Example 687

2-Chloro-5-({4-[2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-[4-(methyl sulfonyl)phenyl]piperidin-1-yl}carbonyl)benzene sulfonamide



10

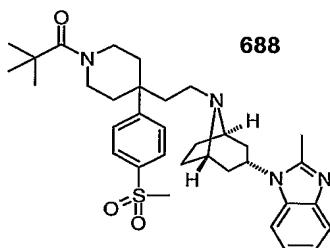
This compound was prepared from 4-(methyl thio)phenylmagnesium bromide and 16a employing methods similar to those described in example 16. The 4-(methylthio)phenyl intermediate corresponding to 16d was oxidized to the methylsulfonyl derivative with MCPBA and converted to compound 687 by methods similar to those outlined in example 16. 1H NMR (400 MHz, CD_3OD) δ 8.02 (d, 2H, J=6 Hz), 7.93 (m, 1H), 7.92 (m, 1H), 7.75 (d, 2H, J=6 Hz), 7.70 (m, 1H), 7.58 (d, 1H, J=7 Hz), 7.50 (d, 1H, J=7 Hz), 7.28 (m, 2H), 4.24 (m, 1H), 3.79 (m, 2H), 3.40 (m, 4H), 3.18 (m, 1H), 3.15 (s, 3H), 2.59 (s, 3H), 2.47 (m, 2H), 2.35 (m, 1H), 2.25-2.00 (m, 12H). HRMS $C_{36}H_{42}ClN_5O_5S_2$ m/z 724.2394 (M+H)_{Cal.}, 724.2372 (M+H)_{Obs.}

15

20

Example 688

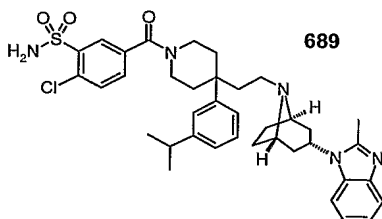
1-[(1R,5S)-8-(2-{1-(2,2-Dimethylpropanoyl)-4-[4-(methylsulfonyl)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



This compound was prepared from 4-(methyl thio)phenylmagnesium bromide and 16a employing methods similar to those described in example 16. The 4-(methylthio)phenyl intermediate corresponding to 16d was oxidized to the methylsulfonyl derivative with MCPBA and converted by methods similar to those outlined in example 16. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.90 (d, 2H, J=8 Hz), 7.68 (d, 2H, J=8 Hz), 7.48 (d, 1H, J=6 Hz), 7.35 (d, 1H, J=7 Hz), 7.10 (m, 2H), 4.50 (m, 1H), 3.75 (m, 2H), 3.27 (m, 4H), 3.20 (s, 3H), 2.50 (s, 3H, obscured by solvent peak), 2.35 (dd, 1H, J=19, 10 Hz), 2.08 (m, 2H), 1.85 (m, 9H), 1.76 (m, 2H), 1.59 (m, 2H), 1.17 (s, 9H). HRMS C₃₄H₄₆N₄O₃S *m/z* 591.3369 (M+H)_{Cal.}, 591.3397 (M+H)_{Obs.}

Example 689

2-Chloro-5-[(4-(3-isopropylphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



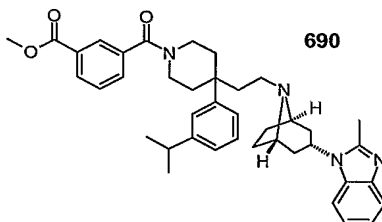
This compound was prepared from 3-isopropyl phenylmagnesium bromide and 16a employing methods similar to those described in example 16. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.93 (s, 1H), 7.68 (d, 1H, J=8 Hz), 7.63

450

(br, 2H), 7.61 (d, 1H, J=8Hz), 7.48 (d, 1H, J=7 Hz), 7.34 (d, 1H, J=7 Hz), 7.27 (t, 1H, J=8 Hz), 7.23 (s, 1H), 7.18 (d, 1H, J=7 Hz), 7.09 (m, 3H), 4.49 (m, 1H), 3.89 (m, 1H), 3.50-3.30 (m, 2H), 3.20 (m, 4H), 2.89 (m, 1H, J=7 Hz), 2.43 (s, 3H), 2.35 (br.dd, 2H, J=22, 10 Hz), 2.17 (m, 1H), 2.07 (m, 1H), 1.90-1.70 (m, 9H), 1.56 (br.d, 2H, J=8Hz), 1.20 (d, 6H, J=7 Hz). HRMS $C_{38}H_{46}ClN_5O_3S$ m/z 688.3088 (M+H)_{Cal.}, 688.3075 (M+H)_{Obs.}.

Example 690

Methyl 3-[(4-(3-isopropylphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzoate

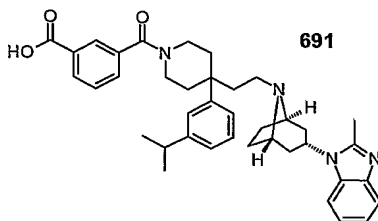


This compound was prepared from 3-isopropyl phenylmagnesium bromide and 16a employing methods similar to those described in example 16. 1H NMR (400 MHz, DMSO- d_6) δ 8.01 (d, 1H, J=7 Hz), 7.91 (s, 1H), 7.67 (d, 1H, J=8 Hz), 7.58 (t, 1H, J=8 Hz), 7.48 (d, 1H, J=7 Hz), 7.34 (d, 1H, J=7 Hz), 7.27 (t, 1H, J=8 Hz), 7.23 (s, 1H), 7.23 (d, 1H, J=8 Hz), 7.09 (m, 3H), 4.49 (m, 1H), 3.89 (m, 1H), 3.84 (s, 3H), 3.43 (m, 1H), 3.37 (m, 1H), 3.21 (m, 3H), 2.89 (m, 1H, J=7 Hz), 2.41 (s, 3H), 2.35 (m, 2H), 2.16 (m, 1H), 2.07 (m, 1H), 1.90-1.70 (m, 10H), 1.59 (br. d, 2H, J=8 Hz), 1.22 (d, 6H, J=8 Hz). HRMS $C_{40}H_{48}N_4O_3$ m/z 633.3805 (M+H)_{Cal.}, 633.3787 (M+H)_{Obs.}.

451

Example 691

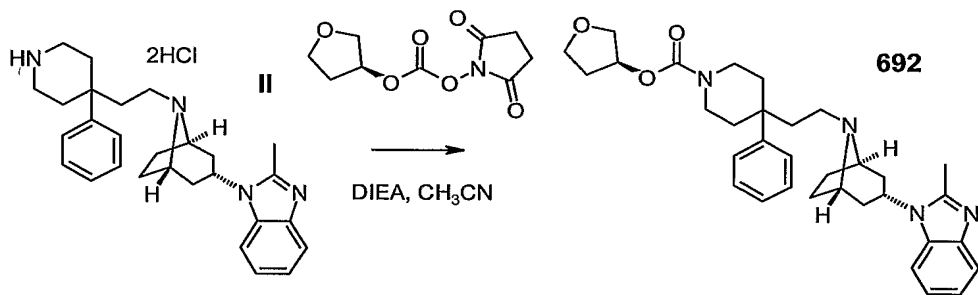
3-[(4-(3-isopropylphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzoic acid



This compound was prepared by hydrolysis of the title compound in example 690 with lithium hydroxide employing methods familiar to those skilled in the art. ¹H NMR (400 MHz, DMSO-d₆) δ 13.1 (br, 1H), 7.99 (d, 1H, J=8 Hz), 7.89 (s, 1H), 7.63 (d, 1H, J=8Hz), 7.56 (t, 1H, J=7 Hz), 7.49 (d, 1H, J=7 Hz), 7.38 (br, 1H), 7.25 (m, 2H), 7.19 (d, 1H, J=8Hz), 7.11 (m, 3H), 4.51 (br, 1H), 3.91 (br, 1H), 3.45 (m, 1H), 3.40-3.20 (m, 4H), 2.89 (m, 1H, J=7 Hz), 2.45 (s, 3H), 2.40-1.60 (m, 16H), 1.20 (d, 6H, J=7 Hz). HRMS C₃₉H₄₆N₄O₃ *m/z* 619.3684 (M+H)_{Cal.}, 619.3643 (M+H)_{Obs.}

Example 692

(3S)-Tetrahydrofuran-3-yl 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxylate

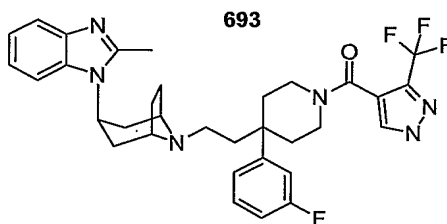


A solution of 1-(([(3S)-tetrahydrofuran-3-yloxy]carbonyl)oxy)pyrrolidine-2,5-dione (US patent 6,344,465) (55 mg, 0.24 mmol), amine dihydrochloride II (100 mg, 0.199 mmol) and *N,N*-diisopropylethylamine (0.14 mL, 0.80 mmol) in acetonitrile (3 mL) was stirred overnight at rt. The solvent was removed at reduced pressure and the remaining material was dissolved in dichloromethane, washed with saturated sodium bicarbonate solution and

dried over magnesium sulfate. Filtration and evaporation of the dichloromethane solution provided the crude product which was purified by chromatography on silica gel eluting with 5% methanol/dichloromethane. Title compound in example 692 was obtained as a white hygroscopic powder (70 mg, 65%). ¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, 1H, J=8 Hz), 7.37 (m, 2H), 7.30-7.20 (m, 4H), 7.16 (m, 2H), 5.25 (m, 1H), 4.61 (m, 1H), 3.85 (m, 4H), 3.73 (m, 2H), 3.22 (m, 4H), 2.58 (br s, 3H), 2.36 (m, 2H), 2.17 (m, 3H), 2.05-1.70 (m, 13H). HRMS C₃₃H₄₂N₄O₃ *m/z* 543.3335 (M+H)_{Cal.}, 543.3331 (M+H)_{Obs.}.

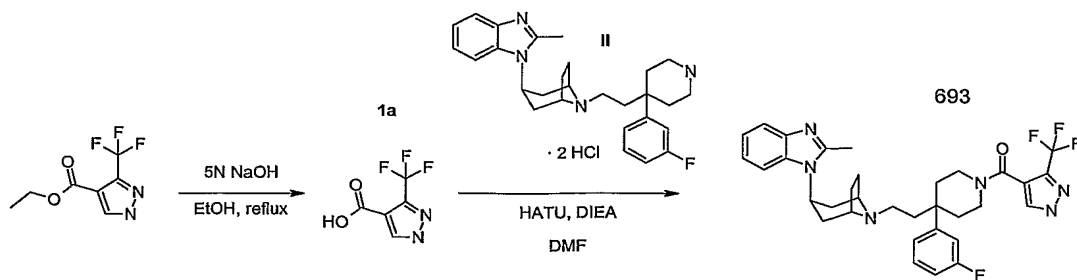
Example 693

1-{8-[2-(4-(3-fluorophenyl)-1-{[3-(trifluoromethyl) pyridin-2-yl]carbonyl}piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole



3-(Trifluoromethyl)-1H-pyrazole-4-carboxylic acid, 1a. A mixture of ethyl 3-(trifluoromethyl)-1H-pyrazole-4-carboxylate (100 mg, 0.48 mmol, 1 eq.), ethanol (5 mL) and 5N NaOH (5 mL) was heated to reflux for 72 h. The reaction was cooled to RT, acidified to pH 2 with 5 N HCl and the product extracted into ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated to provide 3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (1a) as a white solid (80 mg, 93% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 13.95 (broad s, 1H), 8.49 (s, 1H), 3.50 (broad s, 1H). ES-LCMS *m/z* 181.16 (M+H).

453

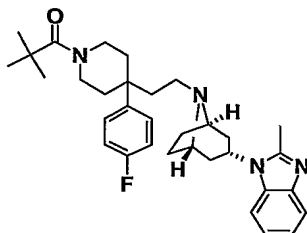


1-{8-[2-(4-(3-fluorophenyl)-1-[[3-(trifluoromethyl)pyridin-2-yl]carbonyl]piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole (example 693). To a solution of 1-(8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride II (130 mg, 0.25 mmol, 1 eq.) in dimethylformamide (4 mL) was added 3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, 1a, (50 mg, 0.27 mmol, 1 eq.) and *N,N*-diisopropylethyl amine (180 μ L, 1.0 mmol, 4 eq.). After stirring at RT for several min, *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uroniumhexafluorophosphate (95 mg, 0.25 mmol, 1 eq.) was added and the reaction was stirred for 2 h. The mixture was partitioned between dichloromethane and satd. aq. NaHCO_3 . The organic layer was dried and concentrated and the residue was purified by prep. HPLC (Method Y) to provide 1-{8-[2-(4-(3-fluorophenyl)-1-[[3-(trifluoromethyl)pyridin-2-yl]carbonyl]piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole 1 as a white solid (30 mg, 20% yield).

^1H NMR (300 MHz, DMSO-d_6) δ 7.65 (m, 2H), 7.32 (m, 2H), 7.16 (m, 2H), 7.07 (m, 1H), 6.97 (m, 2H), 4.62 (m, 1H), 4.18 (m, 1H), 3.50 (m, 1H), 3.27 (m, 4H), 2.52 (m, 3H), 2.45 – 2.09 (m, 4H), 2.04–1.47 (m, 12H). ES-LCMS m/z 609.39 ($\text{M}+\text{H}$). Analytical HPLC (Method W) R_t 2.79 (95.89%).

Example 694

1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(4-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

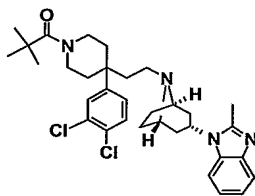


example 694

The title compound was prepared according to procedures analogous to those described for example 16. ¹H NMR (300 MHz, CDCl₃) δ 7.68 (d, 1H, J=2.3 Hz), 7.66 (d, 1H, J=2.2 Hz), 7.32-7.25 (m, 2H), 7.18-7.15 (m, 2H), 7.09-7.04 (m, 2H), 4.68-4.55 (m, 1H), 3.95-3.90 (m, 2H), 3.41-3.20 (m, 4H), 2.57 (s, 3H), 2.43-2.33 (m, 2H), 2.19-2.14 (m, 2H), 1.95-1.62 (m, 12H), 1.26 (s, 9H). LRMS (ES, +ve ion) m/z 531.2 (M+H).

Example 695

1-((1R,5S)-8-{2-[4-(3,4-dichlorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

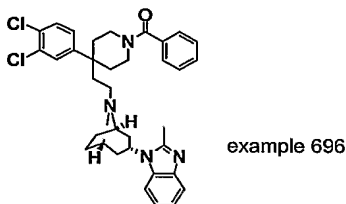


Example 695

The title compound was prepared according to procedures analogous to those described for example 16. ¹H NMR (300 MHz, CDCl₃) δ 7.66 (d, 1H, J=6.9 Hz), 7.45 (d, 1H, J=8.3 Hz), 7.39 (br. s, 1H), 7.32-7.27 (m, 1H), 7.20-7.14 (br. m, 3H), 4.62 (app quint, 1H, J=9.2 Hz), 3.97-3.87 (m, 2H), 3.41-3.25 (m, 4H), 2.58 (s, 3H), 2.44-2.34 (m, 2H), 2.16-2.10 (m, 2H), 1.97-1.65 (m, 12H), 1.27 (s, 9H). LRMS (ES, +ve ion) m/z 581.0 (M+), 583.3 (M+2, ³⁷Cl).

Example 696

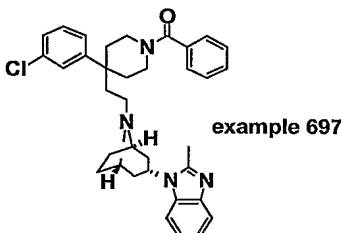
1-((1R,5S)-8-{2-[1-benzoyl-4-(3,4-dichlorophenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



The title compound was prepared according to procedures analogous to those described for example 16. ¹H NMR (300 MHz, CDCl₃) δ 7.66 (d, 1H, J=7.2 Hz), 7.44 (app t) overlapping 7.39 (br s, 8H total), 7.32-7.25 (m) overlapping 7.26 (s, CHCl₃, 2H total), 7.18-7.14 (m, 2H), 4.60 (app quint, 1H, J=8.8 Hz), 4.13 (br s, 1H), 3.57, 3.40, 3.27 (three overlapping br s, 6H total), 2.55 (s, 3H), 2.44-2.34 (m, 2H), 2.21-1.66 (m, 17H). FAB HRMS (calcd for MH⁺, C₃₅H₃₈Cl₂N₄O) 601.2501; Found 601.2501.

Example 697

1-((1R,5S)-8-{2-[1-benzoyl-4-(3-chlorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

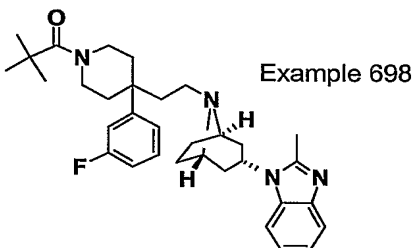


The title compound was prepared according to procedures analogous to those described for example 16. ¹H NMR (300 MHz, CDCl₃) δ 7.66 (d, 1H, J=6.9 Hz), 7.42-7.14 (m, 12H), 4.60 (app quint, 1H, J=9.1 Hz), 4.13 (br s, 1H), 3.56, 3.42 and 3.27 (three overlapping br s, 6H total), 2.55 (s, 3H), 2.44-1.63 (m, 17H). FAB HRMS (calcd for MH⁺, C₃₅H₃₉ClN₄O) 567.2891; Found 567.2885.

456

Example 698

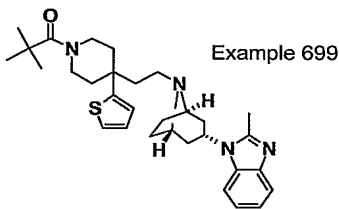
1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



5 The title compound was prepared according to procedures analogous to those described for example 16. ¹H NMR (300 MHz, CDCl₃) δ 7.66 (d, 1H, J=7.2 Hz), 7.38-7.29 (m, 2H), 7.20-6.92 (m, 5H), 4.61 (app quint, 1H, J=8.7 Hz), 3.96 and 3.91 (two overlapping br s, 2H total), 3.42-3.25 (m, 4H), 2.58 (s, 3H), 2.43-2.33 (m, 2H), 2.19-2.12 (m, 2H), 1.96-1.62 (m, 12H), 1.28 (s, 9H).
10 LRMS (ES, +ve ion) m/z 531.3 (M+H).

Example 699

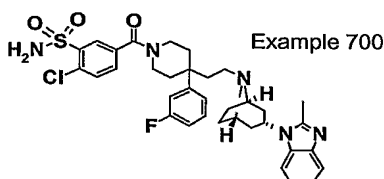
1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-thien-2-yl]piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



15 The title compound was prepared according to procedures analogous to those described for example 16. ¹H NMR (300 MHz, CDCl₃) δ 7.66 (d, 1H, J=6.6 Hz), 7.33-7.15 (m, 4H), 6.99 (app t, 1H, J=4.3 Hz), 6.83 (d, 1H, J=3.3 Hz), 4.64 (app quint, 1H, J=9.0 Hz), 4.09 and 4.04 (two overlapping br s, 2H total), 3.33-3.20 (m, 4H), 2.58 (s, 3H), 2.45-2.34 (m, 2H), 2.20-1.64 (m, 14H),
20 1.28 (s, 9H). LRMS (ES, +ve ion) m/z 518.4 (M+).

Example 700

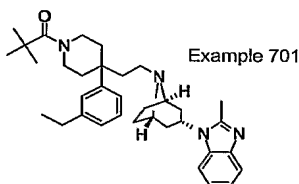
2-chloro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



The title compound was prepared according to procedures analogous to those described for example 16. ¹H NMR (300 MHz, CD₃OD) δ 7.93 (app d, 2H, J=9.6 Hz), 7.78-7.64 (m, 1H), 7.53-7.39 (m, 3H), 7.24-7.15 (m, 4H), 6.99 (app t, 1H, J=8.0 Hz), 4.73 (app quint, 1H, J=9.6 Hz), 4.20-4.15 (br m, 1H), 3.48-3.29 (m) overlapping 3.30 (s, MeOH, 6H total), 3.22-3.14 (m, 1H), 2.52 (s, 3H), 2.48-2.34 (m, 3H), 2.10-1.88 (m, 11H), NH₂ (not observed).

Example 701

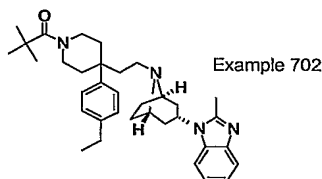
1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(3-ethylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



The title compound was prepared according to procedures analogous to those described for example 16. ¹H NMR (300 MHz, CDCl₃) δ 7.69 (d, 1H, J=7.2 Hz), 7.33-7.08 (m, 7H), 4.68 (app quint, 1H, J=8.8 Hz), 3.98-3.93 (br m, 2H), 3.63 (br m, 2H), 3.36-3.29 (m, 4H), 2.68 (q, 2H, J=7.5 Hz), 2.59 (s, 3H), 2.47-2.37 (m, 2H), 2.26-2.20 (m, 2H), 2.01-1.66 (m, 10H), 1.29 (s) overlapping 1.26 (t, J=7.7 Hz, 12 H total). LRMS (ES, +ve ion) m/z 541.4 (M+H).

Example 702

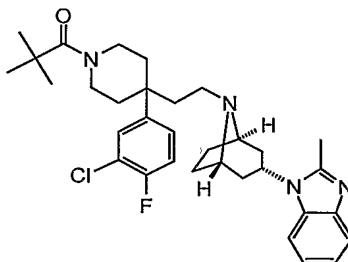
1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(4-ethylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



The title compound was prepared according to procedures analogous to those described for example 16. ¹H NMR (300 MHz, CDCl₃) δ 7.70-7.67 (m, 1H), 7.33-7.28 (m, 1H), 7.22-7.13 (m, 6H), 4.65 (app quint, 1H, J=8.9 Hz), 4.00-3.93 (m, 2H), 3.34-3.26 (m, 4H), 2.66 (q, 2H, J=7.5 Hz), 2.59 (s, 3H), 2.45-2.34 (m, 2H), 2.25-2.19 (m, 2H), 1.96-1.62 (m, 12H), 1.28 (s) overlapping 1.26 (t, J=7.7 Hz, 12 H total). LRMS (ES, +ve ion) m/z 541.4 (M+H).

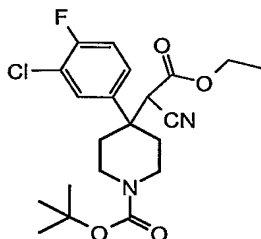
Example 703

Endo 1-((1R,5S)-8-{2-[4-(3-chloro-4-fluorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole was synthesized according to the procedures described in example 16 with a 3-chloro-4-fluoro instead of a 3-chloro substitution in the phenyl ring.

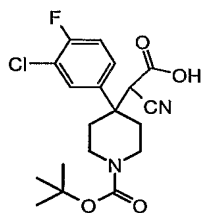


Tert-butyl 4-(3-chloro-4-fluorophenyl)-4-(1-cyano-2-ethoxy-2-oxoethyl)piperidine-1-carboxylate was prepared and used without further purification as described in example 16b from 1-fluoro-2-chloro-4-bromobenzene (10 g, 47.74 mmol) using tetrahydrofuran instead of diethyl ether as a solvent to afford an oil (6.76 g, 100%). ES-LCMS m/z 423 (M-H)⁺.

459



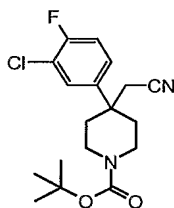
[1-(Tert-butoxycarbonyl)-4-(3-chloro-4-fluorophenyl)piperidin-4-yl](cyano) acetic acid was prepared and used without further purification as described in example 16c (6.76 g, 15.9 mmol) to afford an oil (6.31 g, 100%).



5

Tert-butyl endo 4-(3-chloro-4-fluorophenyl)-4-(cyanomethyl)piperidine-1-carboxylate was prepared as described in example 16d (6.31 g, 15.9 mmol), purified by column chromatography on silica gel, eluting with a gradient of 5-40% ethyl acetate in hexane to afford a beige solid (2.86 g, 51%). ¹H NMR (300 MHz, CDCl₃) δ 7.41 (dd, 1H, J=2.3, 2.5 Hz) 7.30-7.21 (m, 2H), 3.76-3.72 (m, 2H), 3.13 (br t, 2H, J=10.4 Hz), 2.57 (s, 2H), 2.29-2.24 (br m, 2H), 1.93-1.84 (m, 2H), 1.46 (s, 9H). ES-LCMS *m/z* 253 (M-BOC+H)⁺.

10

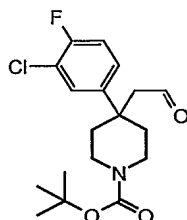


Tert-butyl 4-(3-chloro-4-fluorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate was prepared as described in example 16e from the product obtained in previous step (2.86 g, 8.106 mmol) to afford *tert*-butyl 4-(3-chloro-4-fluorophenyl)-4-(2-oxoethyl)piperidine-1-carboxylate as an oil (2.20 g, 76.2%). ¹H-NMR (300 MHz, CDCl₃) δ 9.45 (t, 1H, J=2.6 Hz), 7.40(dd, 1H, J=2.4 Hz), 7.28-7.20 (m, 2H), 3.66-3.60 (m, 2H), 3.33-3.25 (m, 2H), 2.68 (s, 2H), 2.24-2.17 (br m, 2H), 1.95-1.82 (m, 2H), 1.45 (s, 9H).

15

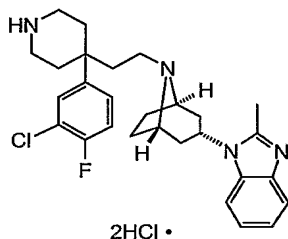
20

460



Tert-butyl 4-(3-chloro-4-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate was prepared as described in example 16f from the product obtained in
 5 previous step (2.20 g, 6.183 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 2-7% methanol in dichloromethane to afford a rigid foam (1.35 g, 61.2%). ¹H-NMR (300 MHz, CDCl₃) δ 7.70 (dd, 1H, J=2, 2.7 Hz), 7.35-7.31 (m, 2H), 7.23-7.11 (m, 4H), 4.72-4.63 (m, 1H), 3.90-3.81 (m, 2H), 3.68-3.63 (br m, 2H), 3.38-3.19 (m, 4H), 3.15-3.00 (m, 1H), 2.61
 10 (s, 3H), 2.55-2.40 (m, 2H), 2.10-1.65 (m, 11H), 1.45 (s, 9H). ES-LCMS *m/z* 581 (M+H)⁺.

Endo 1-((1R,5S)-8-{2-[4-(3-chloro-4-fluoro phenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride was prepared and used without additional purification as described in example 16g
 15 from the product obtained in previous step (1.35 g, 2.26 mmol) to afford a rigid foam (1.28 g, 100%). ES-LCMS *m/z* 481 (M+H)⁺.

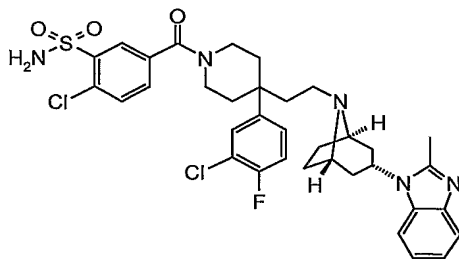


Endo 1-((1R,5S)-8-{2-[4-(3-chloro-4-fluoro phenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (example 703). Title compound in example 703 was
 20 prepared as described in example 16 from endo 1-((1R,5S)-8-{2-[4-(3-chloro-4-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (100 mg, 0.18 mmol), using 3 equivalents of triethylamine and then purified by column chromatography on silica gel,

eluting with a gradient of 2-5% methanol in dichloromethane to afford endo 1-((1R,5S)-8-{2-[4-(3-chloro-4-fluorophenyl)-1-(2,2-dimethylpropanoyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as a rigid foam (40 mg, 39.2 %). ¹H-NMR (300 MHz, CDCl₃) δ 7.69 (d, 1H, J=6.9 Hz), 7.37-7.31 (m, 2H), 7.18-7.14 (m, 4H), 4.75-4.59 (m, 1H), 3.96-3.90 (m, 2H), 3.40-3.32 (m, 4H), 2.60 (s, 3H), 2.47-2.37 (m, 2H), 2.19-2.16 (m, 2H), 2.12-1.79 (m, 8H), 1.70-1.65 (m, 4H), 1.30 (s, 9H). HRMS m/z (M+H) 565.3109 Cal., 565.3104 Obs.

Example 704

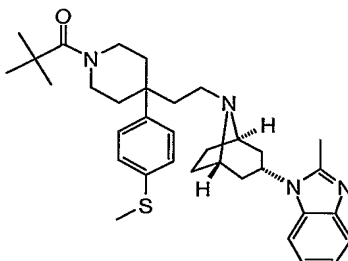
Endo 2-chloro-5-[(4-(3-chloro-4-fluoro phenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide was prepared from endo 1-((1R,5S)-8-{2-[4-(3-chloro-4-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (200 mg, 0.36 mmol) as described in Example 719, purified by column chromatography on silica gel, eluting with a gradient of 0-5% methanol in dichloromethane to afford the title compound as an off white solid (37 mg, 14.6%). ¹H-NMR (300 MHz, CDCl₃) δ 8.14 (s, 1H), 7.69-7.54 (m, 3H), 7.35-7.29 (m, 2H), 7.20-7.15 (m, 4H), 5.41 (br s, 2H), 4.66-4.60 (m, 1H), 4.18-4.10 (m, 1H), 3.51-3.29 (m, 4H), 2.58 (s, 3H), 2.48-2.37 (m, 2H), 2.03-1.67 (m, 15H). HRMS m/z (M+H)⁺ 698.2135 Cal., 698.2132 Obs.



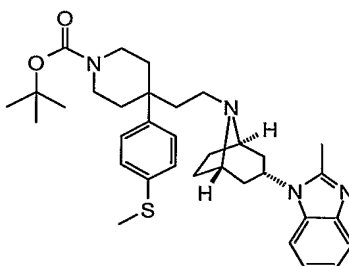
Example 705

Endo 1-[(1R,5S)-8-(2-{1-(2,2-dimethyl propanoyl)-4-[4-(methylthio)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-

1H-benzimidazole was synthesized according to the methods outlined in example 16 with a 4-methylthio instead of a 3-chloro substitution in the phenyl ring.

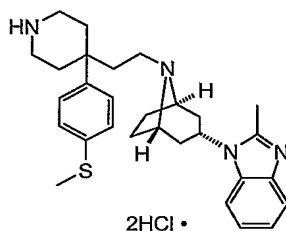


5 Tert-butyl endo 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-[4-(methylthio)phenyl]piperidine-1-carboxylate was prepared as described in example 16f (1.15 g, 3.29 mmol scale) and purified by column chromatography on silica gel, eluting with a gradient of 2.5-5% methanol in dichloromethane to afford an oil (1.39 g, 73.5%). ¹H NMR (300 MHz, CDCl₃) δ 7.70 (d, 1H, J=7 Hz), 7.33-7.15 (m, 7H), 4.78-4.65 (m, 1H), 3.75-3.62 (br m, 2H), 3.38-3.31 (br m, 2H), 3.23-3.15 (m, 2H), 2.60 (s, 3H), 2.51 (s, 3H), 2.48-2.39 (m, 4H), 2.21-2.15 (m, 2H), 1.99-1.66 (m, 10H), 1.46 (s, 9H). ES-LCMS m/z 575 (M+H)⁺.

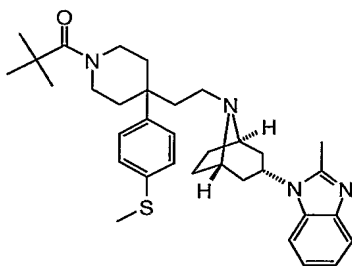


15 Endo 2-methyl-1-[(1R,5S)-8-(2-{4-[4-(methyl thio)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1] oct-3-yl]-1H-benzimidazole dihydrochloride was prepared and used without further purification as described in example 16g from product from previous step (1.39 g, 2.418 mmol) to afford off white solid (1.03 g, 78%). ES-LCMS m/z 475 (M+H)⁺.

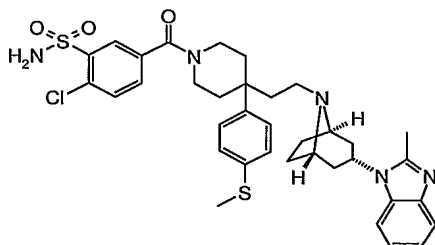
463

Example 705

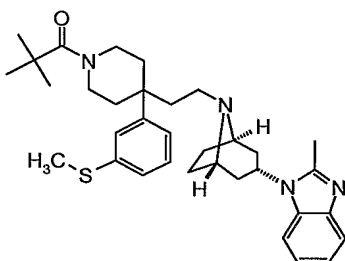
The title compound in example 705 endo 1-[(1R,5S)-8-(2-{1-(2,2-
 5 dimethylpropanoyl)-4-[4-(methyl thio)phenyl]piperidin-4-yl}ethyl)-8-
 azabicyclo[3.2.1] oct-3-yl]-2-methyl-1H-benzimidazole was prepared as
 described in example 16 from the product obtained in previous step (100 mg,
 0.183 mmol), using 3 equivalents of triethylamine and purified by column
 chromatography on silica gel, eluting with a gradient of 1-10% methanol in
 10 dichloromethane to afford beige solid (100.8 mg, 98.8 %). ¹H-NMR (300 MHz,
 CDCl₃) δ 7.69 (d, 1H, J=7.1 Hz), 7.34-7.18 (m, 7H), 4.71-4.57 (m, 1H), 3.99-
 3.94 (m, 2H), 3.32-3.25 (m, 4H), 2.59 (s, 3H), 2.52 (s, 3H), 2.45-2.35 (m, 2H),
 2.28-2.12 (m, 2H), 1.97-1.89 (m, 5H), 1.83-1.75 (m, 4H), 1.68-1.60 (m, 2H),
 1.35 (s, 9H). HRMS m/z (M+H) 559.3471 Cal., 559.3480 Obs.



15

Example 706

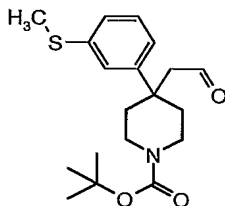
Endo 2-chloro-5-({4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-[4-(methylthio)phenyl]piperidin-1-yl}carbonyl)benzenesulfonamide was prepared from endo 2-methyl-1-[(1R,5S)-8-(2-{4-[4-(methylthio)phenyl] piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole dihydrochloride (200 mg, 0.365 mmol) as described in Example 719 and purified by Plate Purification Method A to afford thick oil (61.4 mg, 24.3%). ¹H-NMR (300 MHz, CDCl₃) δ 8.41 (s, 1H), 7.70 (d, 1H, J=7.1 Hz), 7.61-7.53 (m, 2H), 7.31-7.17 (m, 7H), 4.93-4.86 (m, 1H), 4.19-4.15 (m, 1H), 3.57-3.44 (m, 4H), 3.37-3.27 (m, 2H), 2.59 (s, 3H), 2.52 (s, 3H), 2.46-2.00 (m, 8H), 1.96-1.78 (m, 7H). HRMS m/z (M+H)⁺ 692.2496 Cal., 692.2498 Obs.

Example 707

Endo 1-[(1R,5S)-8-(2-{1-(2,2-dimethyl-propanoyl)-4-[3-(methylthio)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole was synthesized according to the methods described in example 16 with a 3-methylthio instead of a 3-chloro substitution in the phenyl ring.

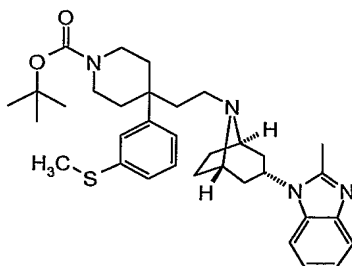
Tert-butyl 4-[3-(methylthio)phenyl]-4-(2-oxoethyl)piperidine-1-carboxylate was prepared and used without further purification as described in example 16e from respective intermediate described in example 720 (2.11 g,

6.09 mmol) to afford *tert*-butyl 4-[3-(methylthio)phenyl]-4-(2-oxoethyl)piperidine-1-carboxylate as an oil (1.14 g, 53.5%). ¹H-NMR (300 MHz, CDCl₃) δ 9.41(t, 1H, J=3 Hz), 7.36-7.26 (m, 1H), 7.17-7.04 (m, 3H), 3.66-3.61 (br m, 2H), 3.32-3.24 (m, 2H), 2.66 (s, 2H), 2.51 (s, 3H), 2.27-2.21 (br m, 2H), 1.91-1.82 (m, 2H), 1.46 (s, 9H).



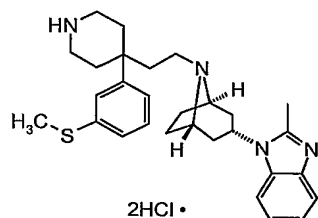
Tert-butyl endo 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-[3-(methylthio)phenyl]piperidine-1-carboxylate

was prepared as described in example 16f from the product obtained in previous step (1.14 g, 3.26 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 0-5% methanol in dichloromethane to afford a rigid foam (0.70 g, 37.3%). ¹H-NMR (300 MHz, CDCl₃) δ 7.70 (d, 1H, J=7 Hz), 7.34-7.08 (m, 7H), 4.70-4.65 (m, 1H), 3.75-3.65 (br m, 2H), 3.35-3.21 (m, 4H), 2.61 (s, 3H), 2.52 (s, 3H), 2.49-2.41 (m, 2H), 2.24-2.18 (m, 2H), 1.99-1.66 (m, 12H), 1.47 (s, 9H). ES-LCMS m/z 575 (M+H)⁺.

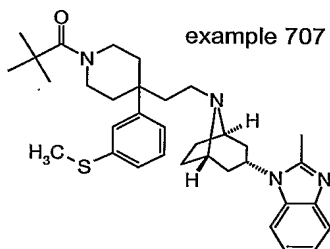


Endo 2-methyl-1-[(1R,5S)-8-(2-{4-[3-(methylthio)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole dihydrochloride was prepared and used without purification as described in example 16g from the product obtained in previous step (0.70 g, 1.217 mmol) to afford off white solid (0.353 g, 100%).

466



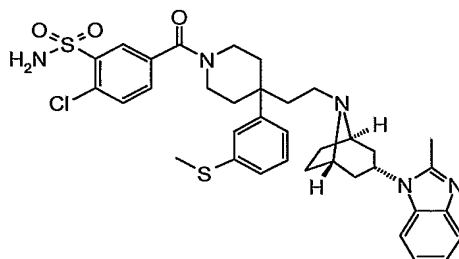
Endo 1-[(1R,5S)-8-(2-{1-(2,2-dimethyl propanoyl)-4-[3-(methylthio)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole was prepared as described in example 16 from the product
5 obtained in previous step (100 mg, 0.1826 mmol), using 3 equivalents of triethylamine and purified by column chromatography on silica gel, eluting with a gradient of 0-5% methanol in dichloromethane to afford colorless oil (64 mg, 63 %). ¹H NMR (300 MHz, CDCl₃) δ 7.69 (d, 1H, J=6.9 Hz), 7.36-7.09 (m, 7H), 4.68-4.60 (m, 1H), 3.98-3.93 (br m, 2H), 3.36-3.29 (m, 4H), 2.60 (s, 3H), 2.53
10 (s, 3H), 2.46-2.35 (m, 2H), 2.33-2.18 (m, 2H), 1.97-1.60 (m, 12H), 1.29 (s, 9H). HRMS m/z (M+H) 559.3471 Cal., 559.3464 Obs.



467

Example 708

endo 2-chloro-5-({4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-[3-(methylthio)phenyl]piperidin-1-yl}carbonyl)benzene sulfonamide



5

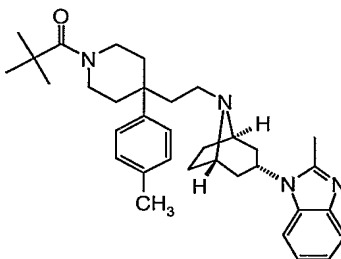
The title compound was prepared as described in Example 719 from dihydrochloride intermediate described in example 707 (200 mg, 0.365 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 3.75-7.50% methanol in dichloromethane with 0.25% ammonium hydroxide to afford white solid (110 mg, 44%). ¹H-NMR (300 MHz, CDCl₃) δ 8.13 (s, 1H), 7.67 (d, 1H, J=6.9Hz), 7.62-7.52 (m, 2H), 7.37-7.32 (m, 2H), 7.28-7.15 (m, 4H), 7.08 (d, 1H, J=7.6 Hz), 5.44 (br s, 2H), 4.71-4.60 (m, 1H), 4.25-4.18 (br m, 1H), 3.58-3.50 (br m, 1H), 3.40-3.27 (br m, 4H), 2.57 (s, 3H), 2.52 (s, 3H), 2.46-2.36 (m, 3H), 2.25-2.16 (br m, 1H), 2.06-1.62 (m, 12H). HRMS m/z (M+H)⁺ 692.2496 Cal., 692.2520 Obs.

10

15

Example 709

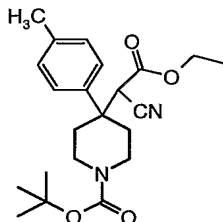
endo 1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(4-methylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



20

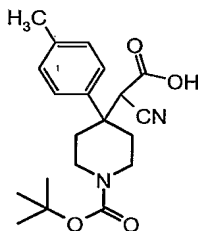
The title compound was synthesized according to the methods described in example 16 with a 4-methyl instead of a 3-chloro substitution in the phenyl ring.

Tert-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-(4-methylphenyl)piperidine-1-carboxylate.



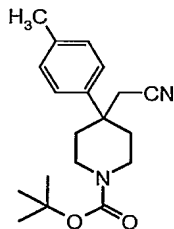
This intermediate was prepared as described in example 16b from 4-bromotoluene (11.97 g, 70 mmol) and using tetrahydrofuran instead of ether as a solvent and purified by column chromatography on silica gel, eluting with 9:1-6:1 hexane-ethyl acetate to afford oily product (5.32 g, 81%). ¹H-NMR (300 MHz, CDCl₃) δ 7.28-7.20 (m, 4H), 4.03-3.92 (m, 4H), 3.57 (s, 1H), 2.93-2.84 (m, 2H), 2.63-2.51 (br m, 2H), 2.36 (s, 3H), 1.45 (s, 9H), 1.05 (t, 3H, J=7.1 Hz). ES-LCMS *m/z* 287 (M-BOC+H)⁺.

[1-(tert-butoxycarbonyl)-4-(4-methylphenyl)piperidin-4-yl](cyano)acetic acid.



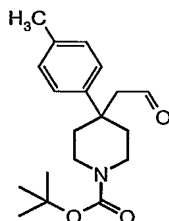
This intermediate was prepared and used without purification as described in example 16c from the product obtained in previous step (5.32 g, 13.76 mmol) to afford rigid foam (4.93 g, 100%). ES-LCMS *m/z* 259 (M-BOC+H).

Tert-butyl 4-(cyanomethyl)-4-(4-methylphenyl)piperidine-1-carboxylate.



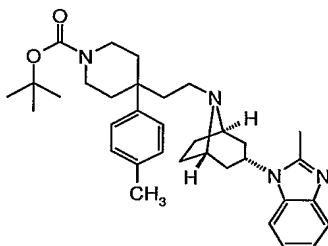
This intermediate was prepared as described in example 16d from the product obtained in previous step (4.93 g, 13.76 mmol) to afford a thick oil (3.51 g, 81%). ¹H-NMR (300 MHz, CDCl₃) δ 7.28-7.21 (m, 4H), 3.80-3.72 (m, 2H), 3.10-3.03 (m, 2H), 2.54 (s, 2H), 2.37 (s, 3H) 2.35-2.31 (m, 2H), 1.89-1.80 (m, 2H), 1.46 (s, 9H). ES-LCMS *m/z* 215 (M-BOC+H)⁺.

Tert-butyl 4-(4-methylphenyl)-4-(2-oxoethyl)piperidine-1-carboxylate.



This intermediate was prepared as described in example 16e from the product obtained in previous step (1.55 g, 4.93 mmol) to afford an oil (1.28g, 82%). ¹H NMR (300 MHz, CDCl₃) δ 9.40 (t, 1H, J=2.9 Hz), 7.28-7.11 (m, 4H), 3.72-3.62 (m, 2H), 3.29-3.20 (m, 2H), 2.63 (s, 2H), 2.54 (s, 3H), 2.36-2.21 (m, 2H), 1.89-1.80 (m, 2H), 1.46 (s, 9H). ES-LCMS *m/z* 218 (M-BOC+H)⁺.

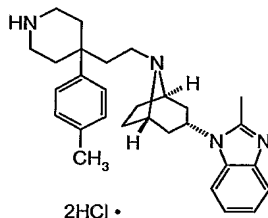
Tert-butyl endo 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(4-methylphenyl)piperidine-1-carboxylate.



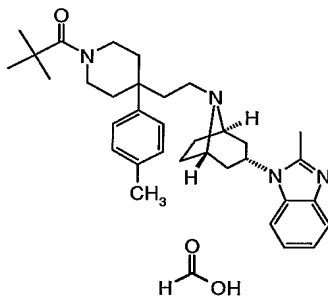
This intermediate was prepared as described in example 16f from the product obtained in previous step (0.60 g, 1.89 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 2-5% methanol in dichloromethane to afford a rigid foam (0.61 g, 59%). ¹H-NMR (300 MHz, CDCl₃) δ 7.70 (d, 1H, J=7.1 Hz), 7.33-7.12 (m, 7H), 4.71-4.65 (m, 1H), 3.75-3.62 (m, 2H), 3.40-3.19 (m, 4H), 2.60 (s, 3H), 2.48-2.25 (m, 2H), 2.36 (s, 3H), 2.22-2.09 (m, 2H), 2.05-1.60 (m, 12H), 1.45 (s, 9H). ES-LCMS *m/z* 543 (M+H)⁺.

470

Endo 2-methyl-1-((1R,5S)-8-{2-[4-(4-methyl phenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole dihydrochloride.



This intermediate was prepared and used without purification, as
 5 described in example 16g from the product obtained in previous step (0.61 g, 1.124 mmol) to afford a white solid (0.579 g, 100%).

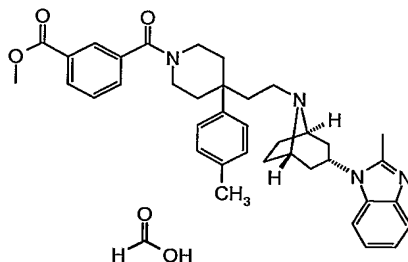


The 1:1 formic acid salt of the title compound from example 709 endo
 1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(4-methylphenyl)piperidin-4-
 10 yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole was prepared
 as described in example 16 from the product obtained in previous step (100
 mg, 0.194 mmol), using 3.2 equivalents of triethylamine and purified by Plate
 Purification Method A to afford a rigid foam (26.65 mg, 26 %). ¹H-NMR (300
 MHz, CDCl₃) δ 8.44 (s, 1H), 7.71 (d, J=7.2 Hz, 1H), 7.30-7.16 (m, 7H), 6.20-
 15 5.80 (br s, 1H), 4.94-4.88 (m, 1H), 3.98-3.93 (m, 2H), 3.51-3.43 (m, 2H), 3.33-
 3.20 (m, 2H), 2.64-2.53 (m, 5H), 2.37 (s, 3H), 2.27-1.72 (m, 14H), 1.28 (s,
 9H). HRMS m/z (M+H) 527.3750 Cal., 527.3745 Obs.

Example 710

formic acid salt (1:1) of endo methyl 3-[4-{2-[(1R, 5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-4-(4-methylphenyl)piperidin-1-yl]carbonyl}benzoate

5 To a solution of the dihydrochloride intermediate obtained in Example



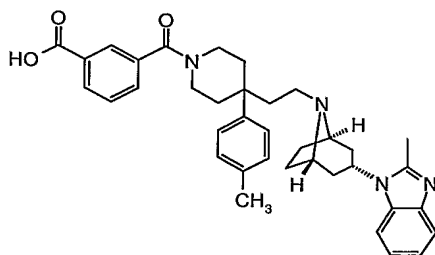
709 (250 mg, 0.485 mmol) in N,N-dimethylformamide (1 ml) was added methylhydrogen isophthalate (87.4 mg, 0.485 mmol), N,N-diisopropylethylamine (0.27 ml, 1.55 mmol) and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (184.3 mg, 0.485 mmol).

10 The reaction mixture was stirred at room temperature for 4h. Quenched by addition of a saturated solution of sodium bicarbonate and extracted with ethyl acetate (3x5 ml). The organic layer was washed with brine and concentrated. The product was purified by column chromatography on silica gel, eluting with a gradient of 2.5-5% methanol in dichloromethane. Further purification was
15 accomplished by Plate Purification Method A to afford a solid product (72.2 mg, 23%).

¹H NMR (300 MHz, CDCl₃) δ 8.43 (br s, 1H), 8.12-8.05 (m, 2H), 7.71 (d, 1H, J=7.3 Hz), 7.61-7.59 (m, 1H), 7.50 (t, 1H, J=7.6 Hz), 7.30-7.23 (m, 7H), 4.96-4.83 (m, 1H), 4.30-4.17 (m, 1H), 3.94 (s, 3H), 3.89-3.80 (m, 4H), 3.43-3.27 (m, 3H), 2.64-2.52 (m, 2H), 2.59 (s, 3H), 2.38(s, 3H), 2.35-1.92 (m, 12H).
20 HRMS m/z (M+H)⁺ 605.3492 Cal., 605.3479 Obs.

Example 711

endo 3-{[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(4-methylphenyl)piperidin-1-yl]carbonyl}benzoic acid



5

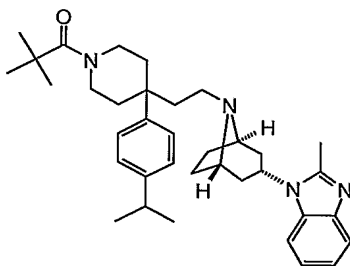
The title compound was prepared as described in example 718 from the product obtained in example 710 (43 mg, 0.0673 mmol) to afford a white solid (35.5 mg, 89.3%). ¹H-NMR (300 MHz, MeOD) δ 8.15-8.11 (m, 1H), 8.05 (s, 1H), 7.60-7.50 (m, 4H), 7.38-7.19 (m, 6H), 5.23-5.13 (m, 1H), 4.23-4.10 (br m, 2H), 3.61-3.57 (br m, 1H), 3.40-3.28 (m, 4H), 2.80-2.60 (m, 4H), 2.59 (s, 3H), 2.42-2.15 (m, 9H), 2.38 (s, 3H), 2.05-1.75 (m, 2H). HRMS m/z (M+H)⁺ 591.3335 Cal., 591.3363 Obs.

10

Example 712

endo 1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(4-isopropylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

15

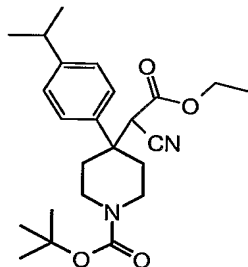


20

The title compound was synthesized according to the methods outlined in example 16 with a 4-isopropyl instead of a 3-chloro substitution in the phenyl ring.

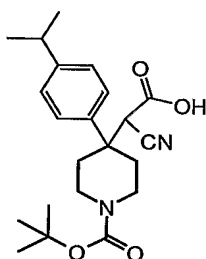
473

Tert-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-(4-isopropylphenyl)piperidine-1-carboxylate.



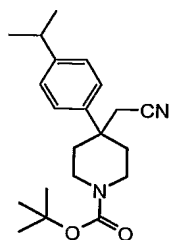
This intermediate was prepared and used without further purification as described in example 16b from 1-bromo-4-isopropylbenzene (10.25 g, 51.48 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 9:1-6:1 hexane-ethyl acetate to afford 3.98g of oil product (56% yield). ES-LCMS m/z 413 ($M+Na$)⁺.

[1-(Tert-butoxycarbonyl)-4-(4-isopropylphenyl)piperidin-4-yl](cyano)acetic acid.



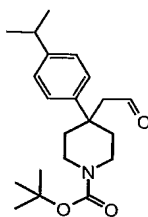
This intermediate was prepared and used without further purification as described in example 16c from the product obtained in previous step (3.98 g, 9.60 mmol) using isopropanol instead of ethanol to afford 3.71 g of oil (100%). ES-LCMS m/z 409 ($M+Na$)⁺.

Tert-butyl 4-(cyanomethyl)-4-(4-isopropylphenyl)piperidine-1-carboxylate.



This intermediate was prepared as described in example 16d from the product from previous step (3.71 g, 9.60 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 10-20% ethyl acetate in hexane to afford an oil which solidified upon standing (2.62 g, 78%). ¹H-NMR (300 MHz, CDCl₃) δ 7.26-7.29 (m, 4H), 3.80-3.72 (m, 2H), 3.17-3.05 (m, 2H), 2.94-2.90 (m, 1H), 2.54 (s, 2H), 2.46-2.32 (m, 2H), 1.91-1.81 (m, 2H), 1.46 (s, 9H), 1.28 (s, 3H), 1.26 (s, 3H).

Tert-butyl 4-(4-isopropylphenyl)-4-(2-oxoethyl)piperidine-1-carboxylate.



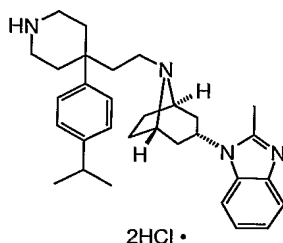
This intermediate was prepared as described in example 16e from the product obtained in previous step (2.62 g, 7.65 mmol) to afford 1.53 g of an oil (58%). ¹H-NMR (300 MHz, CDCl₃) δ 9.40 (t, 1H, J=2.9 Hz), 7.30-7.20 (m, 4H), 3.66-3.61 (br m, 2H), 3.35-3.22 (m, 2H), 2.96-2.87 (m, 1H), 2.64 (d, 2H, J=2.9 Hz), 2.26-2.21 (br m, 2H), 1.90-1.81 (m, 2H), 1.46 (s, 9H), 1.27 (s, 3H), 1.25 (s, 3H). ES-LCMS *m/z* 368 (M+Na)⁺.

tert-butyl endo 4-(4-isopropylphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate.

This intermediate was prepared as described in example 16f from the product obtained in previous step (0.30 g, 0.868 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 2-4% methanol in dichloromethane to afford a rigid foam (0.23 g, 60%). ¹H-NMR (300 MHz, CDCl₃) δ 7.69 (d, 1H, J=7 Hz), 7.33-7.19 (m, 7H), 4.75-4.65 (m, 1H), 3.84-3.65 (m, 2H), 3.39-3.22 (m, 4H), 2.96-2.85 (m, 1H), 2.60 (s, 3H), 2.47-2.37 (m, 2H), 2.16-2.09 (m, 2H), 2.05-1.87 (m, 10H), 1.85-1.80 (m, 2H), 1.45 (s, 9H), 1.29 (s, 3H), 1.27 (s, 3H). ES-LCMS *m/z* 571 (M+H)⁺.

Endo 1-((1R,5S)-8-{2-[4-(4-isopropylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride.

475

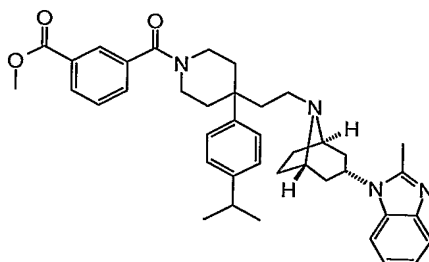


This intermediate was prepared and used without further purification as described in example 16g from the product obtained in previous step (0.23 g, 0.403 mmol) to afford 0.219 g of a white solid (100%). ES-LCMS m/z 443 (M+H)⁺.

Endo 1-((1R,5S)-8-{2-[1-(2,2-dimethyl propanoyl)-4-(4-isopropylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (example 712). The title compound was prepared as described in example 16 from the dihydrochloride intermediate from example 711 (70 mg, 0.1287 mmol), using 3.2 equivalents of triethylamine and purified by column chromatography on silica gel, eluting with a gradient of 2-4% methanol in dichloromethane with 0.1% ammonium hydroxide to afford 49.7 mg of colorless oil. (70%). ¹H-NMR (300 MHz, CDCl₃) δ 7.68 (d, 1H, J=7.0 Hz), 7.33-7.16 (m, 7H), 4.78-4.60 (m, 1H), 3.98-3.93 (m, 2H), 3.36-3.20 (m, 4H), 2.97-2.88 (m, 1H), 2.59 (s, 3H), 2.45-2.35 (m, 2H), 2.24-2.19 (m, 2H), 1.96-1.73 (m, 10H), 1.66-1.64 (m, 2H), 1.29 (s, 9H), 1.28 (s, 3H), 1.26 (s, 3H). HRMS m/z (M+H) 555.4063 Cal., 555.4072 Obs.

Example 713

endo methyl 3-[(4-(4-isopropylphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzoate

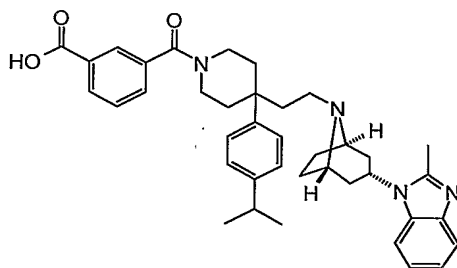


476

The title compound was prepared as described in example 719 from the dihydrochloride described in example 711 (70 mg, 0.1287 mmol) and methylhydrogen isophthalate (23.2 mg, 0.1287 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 2.5-5% methanol in dichloromethane to afford a beige solid (46 mg, 56.4%). ¹H-NMR (300 MHz, CDCl₃) δ 8.11-8.03 (m, 2H), 7.70 (d, 1H, J=7 Hz), 7.62-7.57 (m, 1H), 7.53-7.48 (m, 1H), 7.33-7.15 (m, 7H), 4.71-4.60 (m, 1H), 4.30-4.20 (br s, 1H), 3.94 (s, 3H), 3.45-3.20 (m, 4H), 2.98-2.89 (m, 1H), 2.57 (s, 3H), 2.45-2.19 (m, 4H), 1.97-1.59 (m, 13H), 1.30 (s, 3H), 1.28 (s, 3H). HRMS m/z (M+H)⁺ 633.3804 Cal., 633.3801 Obs.

Example 714

endo 3-[(4-(4-isopropylphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzoic acid

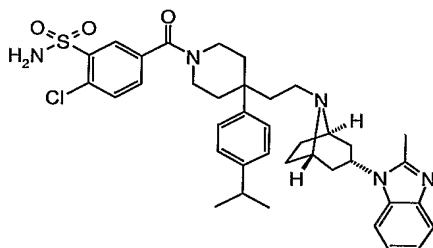


The title compound was prepared as described in example 718 from title compound in example 713 (31 mg, 0.049 mmol) and purified by Plate Purification Method A to afford white solid (10.4 mg, 34.3%). ¹H-NMR (300 MHz, MeOH-d₄) δ 8.31 (s, 1H), 8.14 (t, 1H, J=3.3 Hz), 8.05 (s, 1H), 7.59-7.56 (m, 3H), 7.49 (d, 1H, J=6.7 Hz), 7.37-7.22 (m, 5H), 5.19-5.12 (m, 1H), 4.19-4.15 (br m, 2H), 3.89-3.82 (br m, 2H), 3.59-3.54 (m, 1H), 3.39-3.27 (m, 4H), 2.99-2.88 (m, 1H), 2.77-2.67 (br m, 2H), 2.59-2.45 (m, 2H), 2.56 (s, 3H), 2.37-1.80 (m, 10H), 1.27 (s, 3H), 1.25 (s, 3H). HRMS m/z (M+H)⁺ 619.3648 Cal., 619.3647 Obs.

Example 715

endo 2-chloro-5-[(4-(4-isopropylphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1] oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzene sulfonamide

5



The title compound was prepared as described in Example 719 from dihydrochloride intermediate described in example 711 (100 mg, 0.184 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 2-4% methanol in dichloromethane with 1% ammonium hydroxide to afford an off white solid (43.2 mg, 34%). ¹H-NMR (300 MHz, CDCl₃) δ 8.13 (s, 1H), 7.67 (d, 1H, J=7Hz), 7.61-7.52 (m, 3H), 7.33-7.13 (m, 6H), 5.42 (br s, 2H), 4.67-4.61 (m, 1H), 4.24-4.18 (br m, 1H), 3.55-3.42 (br m, 1H), 3.38-3.20 (br m, 4H), 3.00-2.91 (m, 1H), 2.57 (s, 3H), 2.45-2.35 (m, 4H), 2.27-2.21 (br m, 1H), 1.98-1.70 (m, 11H), 1.28 (s, 3H), 1.26 (s, 3H). HRMS m/z (M+H)⁺ 688.3088 Cal., 688.3079 Obs.

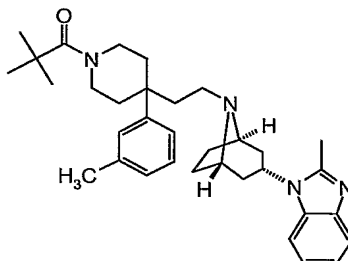
10

15

478

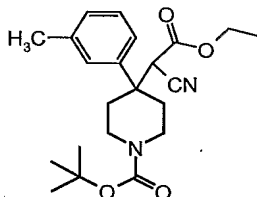
Example 716

endo 1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(3-methylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



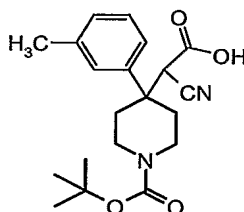
The title compound was synthesized according to the methods outlined in example 16 with a 3-methyl instead of a 3-chloro substitution in the phenyl ring.

Tert-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-(3-methylphenyl)piperidine-1-carboxylate.



This intermediate was prepared and used without further purification as described in example 16b from 3-bromotoluene (11.97 g, 70 mmol) to afford 6.13g of an oil (93.4%). ES-LCMS m/z 287 (M-BOC+H)⁺.

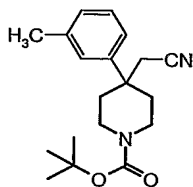
[1-(Tert-butoxycarbonyl)-4-(3-methylphenyl)piperidin-4-yl](cyano)acetic acid.



This intermediate was prepared as described in example 16c from the product obtained in previous step (6.13 g, 15.86 mmol) and was used without further purification to afford 5.68 g of an oil (100%). ES-LCMS m/z 259 (M-BOC+H)⁺.

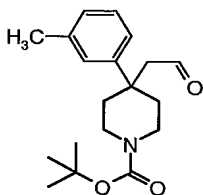
Tert-butyl 4-(cyanomethyl)-4-(3-methylphenyl) piperidine-1-carboxylate.

479



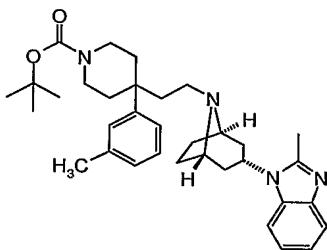
This intermediate was prepared as described in example 16d from the product obtained in previous step (5.68 g, 15.86 mmol) to afford 2.66 g of an oil (2.66 g, 53.3%). ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.28 (m, 1H), 7.18-7.12 (m, 3H) 3.82-3.72 (m, 2H), 3.13-3.04 (m, 2H), 2.55 (s, 2H), 2.39 (s, 3H) 2.37-2.31 (m, 2H), 1.91-1.82 (m, 2H), 1.46 (s, 9H). ES-LCMS *m/z* 215 (M-BOC+H)⁺.

Tert-butyl 4-(3-methylphenyl)-4-(2-oxoethyl)piperidine-1-carboxylate.



This intermediate was prepared as described in example 16e from the product described in previous step (2.66 g, 8.46 mmol) to afford 2.24g of an oil (83%). ¹H-NMR (300 MHz, CDCl₃) δ 9.39 (t, 1H, J=2.9 Hz), 7.31-7.28 (m, 1H), 7.20-7.07 (m, 3H), 3.68-3.60 (m, 2H), 3.31-3.22 (m, 2H), 2.64 (s, 2H), 2.38 (s, 3H), 2.27-2.21 (m, 2H), 1.90-1.81 (m, 2H), 1.46 (s, 9H).

Tert-butyl endo-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl)piperidine-1-carboxylate.

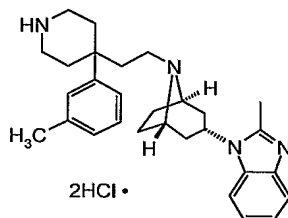


This intermediate was prepared as described in example 16f from the product obtained in previous step (0.60 g, 1.89 mmol) and purified by column chromatography on silica gel, eluting with 5% methanol in dichloromethane to afford 0.58 g of a rigid foam (0.58 g, 57%). ¹H-NMR (300 MHz, CDCl₃) δ 7.70-7.68 (d, 1H, J=7 Hz), 7.34-7.04 (m, 7H), 4.73-4.63 (m, 1H), 3.70-3.66 (m,

480

2H), 3.30-3.21 (m, 4H), 2.60 (s, 3H), 2.46-2.32 (m, 2H), 2.39 (s, 3H), 2.18-2.09 (m, 2H), 2.00-1.90 (m, 6H), 1.85-1.75 (m, 4H), 1.73-1.60 (m, 2H), 1.44 (s, 9H). ES-LCMS m/z 543 (M+H)⁺.

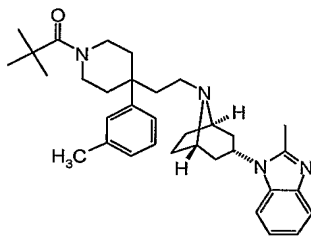
5 *Endo 2-methyl-1-((1R,5S)-8-{2-[4-(3-methyl phenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole dihydrochloride.*



This intermediate was prepared and used without further purification as described in example 16g from the product obtained in previous step (0.58 g, 1.068 mmol) to afford 0.55g of a white solid (100%). ES-LCMS m/z 443 (M+H)⁺.

Example 716

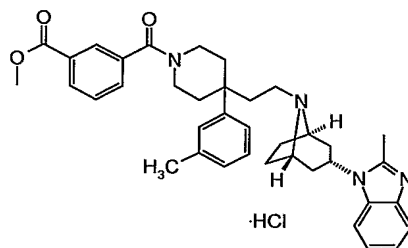
endo 1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(3-methylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1] oct-3-yl)-2-methyl-1H-benzimidazole



15 The title compound was prepared as described in example 16 from the product obtained in previous step (100 mg, 0.194 mmol), using 3.2 equivalents of triethylamine to afford 33 mg of a colorless oil (32%). ¹H NMR (300 MHz, CDCl₃) δ 7.69 (d, 1H, J=7.1 Hz), 7.33-7.06 (m, 7H), 4.70-4.50 (m, 1H), 3.99-3.94 (m, 2H), 3.36-3.20 (m, 4H), 2.60 (s, 3H), 2.50-2.35 (m, 2H), 2.40 (s, 3H), 2.24-2.20 (m, 2H), 1.96-1.60 (m, 12H), 1.30 (s, 9H). HRMS m/z (M+H)⁺ 527.3750 Cal., 527.3769 Obs.

Example 717

endo methyl 3-[[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl)piperidin-1-yl]carbonyl]benzoate hydrochloride

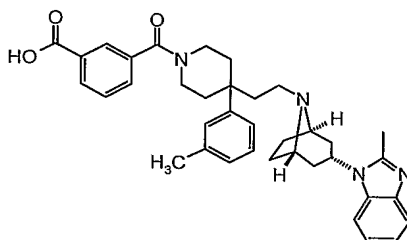


To a solution of methyl hydrogen isophthalate (70 mg, 0.3879 mmol) in dichloromethane (4 ml) was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (74.36 mg, 0.3879 mmol), 1-hydroxybenzotriazole (52.42 mg, 0.3879 mmol), endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo [3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride II (200 mg, 0.3879 mmol) and N,N-diisopropylethylamine (0.225 ml, 1.29 mmol). After stirring at room temperature overnight, 10% citric acid (5 ml) was added to the mixture and extracted with dichloromethane (2 x 10 ml). The combined organic phase was washed with water (10 ml) and dried over anhydrous sodium sulfate.

After evaporation of the solvent the product was purified by column chromatography on silica gel, eluting with 2% methanol in dichloromethane and then treated with 4M HCl-dioxane solution (1.2 ml) to afford endo methyl 3-[[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl)piperidin-1-yl]carbonyl]benzoate hydrochloride as a rigid white foam (94 mg, 38%). ¹H NMR (300 MHz, CDCl₃) δ 12.19 (br s, 1H), 8.11-8.03 (m, 2H), 7.70-7.48 (m, 3H), 7.31-7.11 (m, 7H), 4.69-4.60 (m, 1H), 4.21-4.19 (m, 1H), 3.94 (s, 3H), 3.61-3.29 (m, 3H), 2.58 (s, 3H), 2.43-2.25 (m, 4H), 2.39 (s, 3H), 2.18-2.15 (m, 2H), 1.96-1.76 (m, 10H), 1.67-1.60 (m, 2H). HRMS m/z (M+H)⁺ 605.3524 Cal., 605.3484 Obs.

Example 718

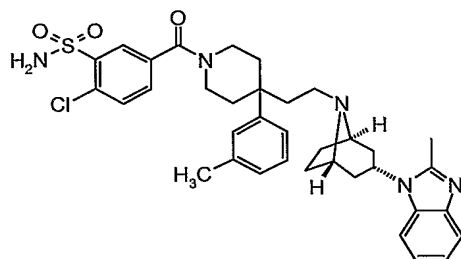
endo 3-{[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl)piperidin-1-yl]carbonyl}benzoic acid



5 To a solution of the compound obtained in Example 717 (51 mg, 0.0795 mmol) in a 1:1 mixture of diethyl ether- methanol (2ml), was added a 2M solution of sodium hydroxide (0.3 ml). The reaction mixture was heated at 50°C for 30 minutes and allowed to cool to room temperature. A solution of 1N hydrochloric acid was added to adjust pH to 5 and the resulting mixture
10 was extracted with dichloromethane (3x5 ml). After drying over sodium sulfate, the solution was concentrated to afford 42.5 mg of a rigid white foam (90.4%). ¹H-NMR (300 MHz, MeOH-d₄) δ 8.12-8.08 (m, 1H), 8.01 (s, 1H), 7.57-7.44 (m, 4H), 7.36-7.15 (m, 5H), 7.10 (d, 1H, J=7.1 Hz), 5.00-4.82 (m, 1H), 4.19-4.15 (m, 1H), 3.58-3.49 (m, 3H), 3.43-3.33 (m, 3H), 2.61-2.40 (m, 2H), 2.55 (s, 3H), 2.38 (s, 3H), 2.27-2.17 (m, 2H), 2.15-1.95 (m, 10H), 1.90-1.78 (m, 2H). HRMS m/z (M+H)⁺ 591.3313 Cal., 591.3345 Obs.

Example 719

endo 2-chloro-5-([4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl)piperidin-1-yl]carbonyl}benzene sulfonamide



5

To a solution of endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride (200 mg, 0.3879 mmol) in N,N-dimethylformamide (1.5 ml) was added 4-chloro-3-sulfamoylbenzoic acid (91.4 mg, 0.3879 mmol), triethylamine (0.163 ml, 1.1637 mmol) and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (162.2 mg, 0.4267). The reaction mixture was stirred at room temperature for 2h. Water was added until a precipitate formed, after filtration the resulting solid was washed with saturated sodium bicarbonate solution (10 ml) and water (10 ml). The product was purified by column chromatography on silica gel, eluting with 5% methanol in dichloromethane with 0.5% ammonium hydroxide to afford endo 2-chloro-5-([4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl) piperidin-1-yl]carbonyl}benzenesulfonamide as a white solid (115 mg, 45%). ¹H-NMR (300 MHz, CDCl₃) δ 7.92-7.83 (m, 1H), 7.74-7.66 (m, 1H), 7.57-7.49 (m, 1H), 7.33-7.07 (m, 8H), 5.44 (br s, 2H), 4.69-4.62 (m, 1H), 4.35-4.23 (m, 1H), 3.42-3.16 (m, 6H), 2.55 (s, 3H), 2.45-2.30 (m, 2H), 2.35 (s, 3H), 2.28-2.18 (m, 1H), 2.05-1.60 (m, 12H). HRMS m/z (M+H)⁺ 660.2775 Cal., 660.2772 Obs.

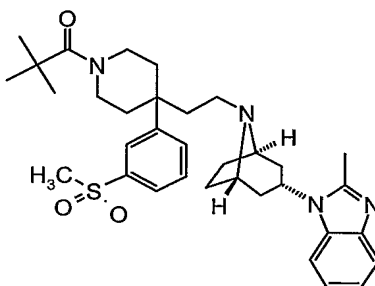
10

15

20

Example 720

endo 1-[(1R,5S)-8-(2-{1-(2,2-dimethylpropanoyl)-4-[3-(methylsulfonyl)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

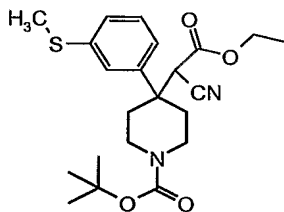


5

Title compound in example 720 was synthesized according to the methods outlined in example 16 with a 3-methylsulfonyl instead of a 3-chloro substitution in the phenyl ring.

Tert-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-[3-(methylthio)phenyl]piperidine-1-carboxylate.

10

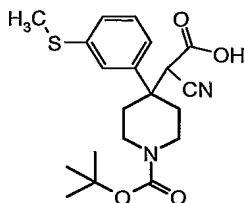


This intermediate was prepared as described in example 16b from 3-bromothioanisole (4.56 g, 22.45 mmol) and using tetrahydrofuran instead of diethyl ether as a solvent and purified by column chromatography on silica gel, eluting with a gradient of 9:1-6:1 hexane-ethyl acetate to afford *tert*-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-[3-(methylthio)phenyl]piperidine-1-carboxylate as an oil (1.61 g, 71%). ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.14 (m, 4H), 4.01-3.82 (m, 4H), 3.59 (s, 1H), 2.95-2.87 (m, 2H), 2.62-2.50 (m, 2H), 2.51 (s, 3H) 2.17-1.97 (m, 2H), 1.46 (m, 9H). ES-LCMS *m/z* 417 (M-H)⁻.

20

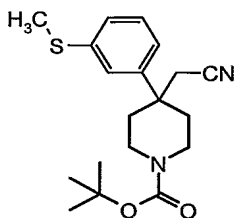
{1-(tert-butoxycarbonyl)-4-[3-(methylthio)phenyl]piperidin-4-yl}(cyano)acetic acid.

485



This intermediate was prepared and used without further purification as described in example 16c from the product obtained in previous step (1.61 g, 3.846 mmol) to afford 1.50g of an oil (100%).

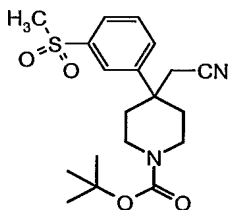
5 *Tert-butyl 4-(cyanomethyl)-4-[3-(methylthio)phenyl]piperidine-1-carboxylate.*



This intermediate was prepared as described in example 16d from the product from previous step (1.50 g, 3.846 mmol) and purified by column

10 chromatography on silica gel, eluting with a gradient of 10-20% ethyl acetate in hexane to afford 1.13 g of an oil (yield 85%). ¹H-NMR (300 MHz, CDCl₃) δ 7.39-7.15 (m, 4H), 3.80-3.70 (br m, 2H), 3.14-3.06 (m, 2H), 2.56 (s, 2H), 2.52 (s, 3H), 2.35-2.30 (m, 2H), 1.92-1.83 (m, 2H), 1.46 (s, 9H).

15 *Tert-butyl 4-(cyanomethyl)-4-[3-(methylsulfonyl)phenyl]piperidine-1-carboxylate.*

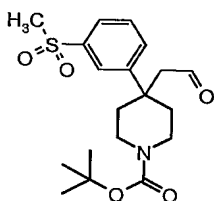


To a solution of product from previous step (1.13 g, 3.26 mmol) in dichloromethane (5 ml) cooled in an ice bath to 0°C, was added a solution of m-chloroperbenzoic acid (1.46 g, 8.48 mmol) in dichloromethane (15 ml) dropwise. The mixture was stirred at 0°C for 1h and a 5% solution of sodium thiosulfate in saturated sodium bicarbonate (50 ml) was then added. The

20

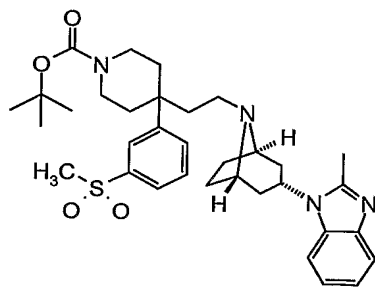
resulting mixture was allowed to stir at room temperature for 30 minutes and extracted with dichloromethane (50 ml). The combined organic phase was washed with 1N NaOH (2x30 ml), water (2x20 ml), dried over anhydrous sodium sulfate and concentrated the solvent to afford *tert*-butyl 4-(cyanomethyl)-4-[3-(methylsulfonyl)phenyl] piperidine-1-carboxylate as a rigid foam (1.05 g, 85%). AP-LCMS m/z 279 (M-BOC+H)⁺. This material was used without further purification.

Tert-butyl 4-[3-(methylsulfonyl)phenyl]-4-(2-oxoethyl)piperidine-1-carboxylate.



This intermediate was prepared as described in example 16e from the product obtained in previous step (1.05 g, 2.774 mmol) to afford 0.69g of a rigid foam (yield 65%), which was used further without additional purification. AP-LCMS m/z 282 (M-BOC+H)⁺.

Tert-butyl endo 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-[3-(methylsulfonyl)phenyl]piperidine-1-carboxylate.

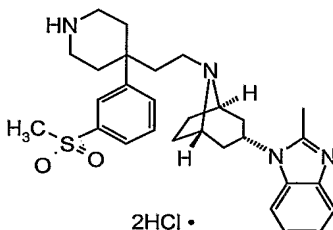


This intermediate was prepared as described in example 16f from the product obtained in previous step (0.69 g, 1.808 mmol) and purified by column chromatography on silica gel, eluting with 5% methanol in dichloromethane to afford 0.37 g of an oil (yield 34%). ¹H-NMR (300 MHz, CDCl₃) δ 7.94 (s, 1H), 7.90-7.83 (m, 1H), 7.70-7.61(m, 3H), 7.34-7.28 (m, 1H), 7.19-7.14 (m, 2H), 4.68-4.61 (m, 1H), 3.70-3.64 (m, 2H), 3.32-3.21 (m, 4H), 3.10 (s, 3H), 2.61 (s,

487

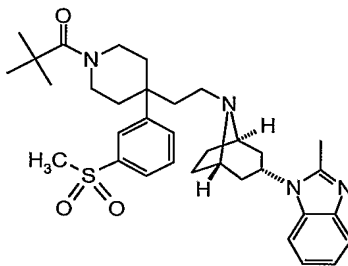
3H), 2.50-2.38 (m, 2H), 2.25-2.17 (m, 2H), 2.05-1.78 (m, 8H), 1.70-1.57 (m, 4H), 1.45 (s, 9H). ES-LCMS m/z 607 ($M+H$)⁺.

Tert-butyl endo 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-[3-(methylsulfonyl)phenyl]piperidine-1-carboxylate dihydrochloride.



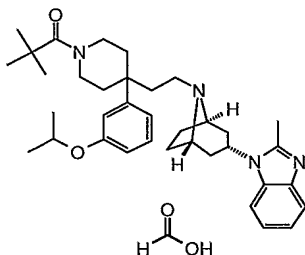
This intermediate was prepared as described in example 16g from the product from previous step (0.37 g, 0.6097 mmol) to afford the dihydrochloride as white solid (0.353 g, 100%). ES-LCMS m/z 507 ($M+H$)⁺. This material was used without further purification.

Endo 1-[(1R,5S)-8-(2-{1-(2,2-dimethyl propanoyl)-4-[3-(methylsulfonyl)phenyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole.



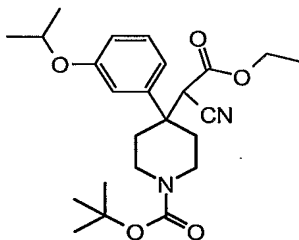
The title compound in example 720 was prepared as described in example 16 from the product obtained in previous step (100 mg, 0.1725 mmol), using 3.2 equivalents of triethylamine to afford 65.4 mg of a colorless oil (yield 64 %). ¹H-NMR (300 MHz, CDCl₃) δ 7.94 (s, 1H), 7.88-7.83 (m, 1H), 7.70-7.60 (m, 3H), 7.33-7.28 (m, 1H), 7.20-7.14 (m, 2H), 4.71-4.58 (m, 1H), 3.94-3.88 (m, 2H), 3.51-3.40 (m, 2H), 3.28-3.20 (m, 1H), 3.11 (s, 3H), 2.61 (s, 3H), 2.47-2.37 (m, 2H), 2.30-2.18 (m, 2H), 2.05-1.90 (m, 10H), 1.75-1.58 (m, 3H), 1.41 (s, 9H). HRMS m/z ($M+H$) 591.3369 Cal., 591.3369 Obs.

Example 721



Formic acid salt of endo1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(3-isopropoxyphenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (1:1) was synthesized according to the methods outlined in example 16 with a 3-isopropoxy instead of a 3-chloro substitution in the phenyl ring.

Tert-butyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-(3-isopropoxyphenyl)piperidine-1-carboxylate.

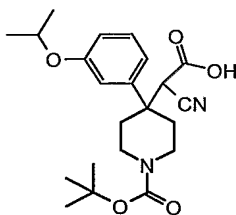


10

This intermediate was prepared as described in example 16b from 1-bromo-3-isopropoxybenzene (10 g, 46.5 mmol) using tetrahydrofuran instead of diethyl ether as a solvent and purified by column chromatography on silica gel, eluting with a gradient of 9:1-6:1 ethyl acetate in hexane to afford 4.68 g of an oil (yield 70%). ES-LCMS m/z 453 ($M+Na$)⁺. This material was used without further purification.

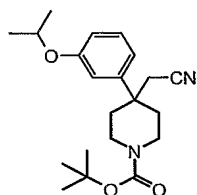
15

[1-(Tert-butoxycarbonyl)-4-(3-isopropoxyphenyl)piperidin-4-yl](cyano)acetic acid.



This intermediate was prepared and used without further purification as described in example 16c from the product obtained in previous step (4.68 g, 10.87 mmol) to afford 4.37g of an oil (yield 100%). ES-LCMS m/z 303 (M-BOC+H)⁺.

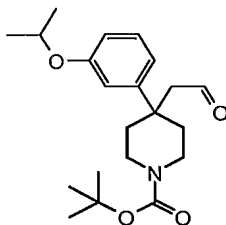
5 *Tert-butyl 4-(cyanomethyl)-4-(3-isopropoxyphenyl)piperidine-1-carboxylate.*



This intermediate was prepared as described in example 16d from the product obtained in previous step (4.37 g, 10.87 mmol) and purified by column

10 chromatography on silica gel, eluting with a gradient of 10-20% ethyl acetate in hexane to afford 2.45 g of an oil (yield 62.5%). ¹H-NMR (300 MHz, CDCl₃) δ 7.32 (t, 1H, J=8 Hz), 6.93 (d, 1H, J=7.9 Hz), 6.89 (s, 1H), 6.83 (d, 1H, J=5.9 Hz), 4.61-4.53 (m, 1H), 3.81-3.72 (br m, 2H), 3.12-3.04 (m, 2H), 2.54 (s, 2H), 2.34-2.29 (m, 2H), 1.89-1.80 (m, 2H), 1.46 (s, 9H), 1.37 (s, 3H), 1.35 (s, 3H).
 15 ES-LCMS m/z 259 (M-BOC+H)⁺.

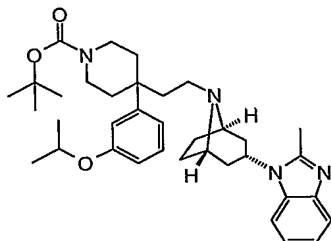
Tert-butyl 4-(3-isopropoxyphenyl)-4-(2-oxoethyl)piperidine-1-carboxylate.



This intermediate was prepared and used without further purification as described in example 16e from the product obtained in previous step (2.45 g, 6.834 mmol) to afford 1.96 g of an oil (yield 79.3%).

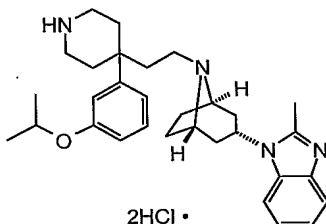
20 *Tert-butyl endo 4-(3-isopropoxyphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}piperidine-1-carboxylate.*

490



This intermediate was prepared as described in example 16f from the product obtained in previous step (1.96 g, 5.422 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 0-10% methanol in dichloromethane to afford 1.42g of a rigid foam (yield 46.4%). ¹H-NMR (300 MHz, CDCl₃) δ 7.70 (d, 1H, J=7.2 Hz), 7.30-7.15 (m, 3H), 6.93-6.70 (m, 4H), 4.74-4.61 (br m, 1H), 4.59-4.53 (m, 1H), 3.68-3.64 (br m, 2H), 3.35-3.00 (m, 4H), 2.61 (s, 3H), 2.57-2.41 (m, 2H), 2.20-2.15 (m, 2H), 2.05-1.60 (m, 12H), 1.46 (s, 9H), 1.37 (s, 3H), 1.35 (s, 9H).

Endo 1-((1R,5S)-8-{2-[4-(3-isopropoxyphenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride.



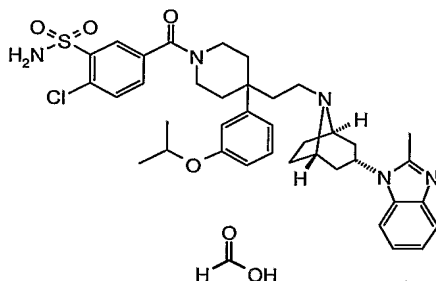
This intermediate was prepared and used without purification as described in example 16g from the product obtained in previous step (1.42 g, 2.42 mmol) to afford 1.32 g of a rigid foam (yield 97.5%). ES-LCMS *m/z* 487 (M + H)⁺.

Formic acid salt of *endo 1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-(3-isopropoxyphenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole*. The title compound in example 721 was prepared as described in example 16 from the product obtained in previous step (100 mg, 0.179 mmol), using 3 equivalents of triethylamine and purified by Plate Purification Method A to afford 21.2 mg of a colorless oil (yield 21 %). ¹H-NMR (300 MHz, CDCl₃) δ 8.46 (s, 1H), 7.70 (d, 1H, J=7.2 Hz), 7.32-7.15 (m, 4H), 6.93-6.78 (m, 3H), 4.85-4.76 (m, 1H), 4.62-4.54 (m, 1H), 3.98-3.93 (br m, 2H), 3.46-3.40 (br m, 2H), 3.36-3.28 (m, 2H), 2.60 (s, 3H), 2.57-2.46 (m, 2H),

2.21-1.73 (m, 14H), 1.39 (s, 3H), 1.37 (s, 3H), 1.30 (s, 9H). HRMS m/z (M+H) 571.4012 Cal., 571.4014 Obs.

Example 722

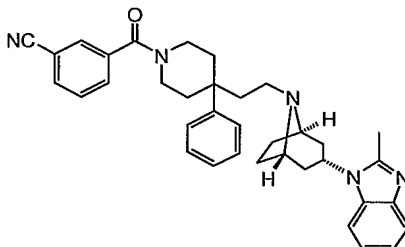
5 formic acid salt (1:1) of endo 2-chloro-5-[(4-(3-isopropoxyphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



The title compound in example 722 was prepared as described in
10 Example 719 from dihydrochloride described in example 721 (200 mg, 0.357 mmol) and purified by Plate Purification Method A to afford a 1:1 salt of a formic acid and endo 2-chloro-5-[(4-(3-isopropoxyphenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide as an off-white solid (34 mg, 13%). ¹H-NMR (300 MHz, CDCl₃) δ 8.41 (br s, 1H), 8.13 (s, 1H), 7.70 (d, 1H, J=7.2 Hz), 7.62-7.53 (m, 1H), 7.59 (s, 1H), 7.34-7.24 (m, 2H), 7.20-7.15 (m, 2H), 6.87-6.80 (m, 3H), 4.83-4.77 (m, 1H), 4.65-4.52 (m, 1H), 4.22-4.19 (br m, 1H), 3.50-3.27 (m, 4H), 2.59 (s, 3H), 2.56-2.46 (m, 2H), 2.20-1.83 (m, 15H), 1.80-1.75 (m, 2H), 1.37 (s, 3H), 1.35 (s, 3H). HRMS m/z (M+H)⁺ 704.3037 Cal., 704.3055
15 Obs.
20

Example 723

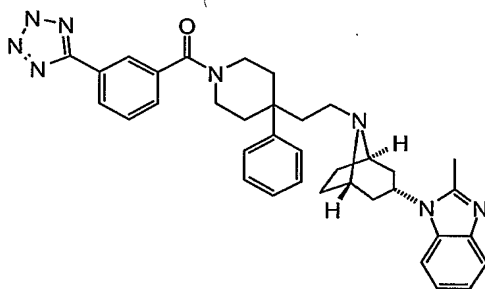
endo 3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzonitrile



5 To a solution of 1,1'-carbonyldiimidazole (68.1 mg, 0.42 mmol) and 3-cyanobenzoic acid (51.5 mg, 0.35 mmol) in dichloromethane (6 ml) was added endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole II and converted to the free base (0.15 g, 0.35 mmol). The mixture was stirred at room temperature for 4h and
10 water (5 ml) was then added. The resultant mixture was extracted with dichloromethane (3x5 ml) and washed with saturated sodium bicarbonate (1x5 ml) and brine (1x5 ml). After drying over sodium sulfate, the solution was concentrated and purified by column chromatography on silica gel, eluting with 5% methanol in dichloro-methane to afford 70 mg of a colorless oil (yield
15 36%). ¹H NMR (300 MHz, CDCl₃) δ 7.74-7.22 (m, 11H), 7.20-7.13 (m, 2H), 4.69-4.55 (m, 1H), 4.30-4.20 (br m, 1H), 3.40-3.19 (m, 4H), 2.58 (s, 3H), 2.44-2.37 (m, 3H), 2.34-2.06 (br m, 1H), 1.96-1.84 (m, 11H), 1.65-1.60 (m, 2H). HRMS *m/z* (M+H) 558.3166 Cal., 558.3252 Obs.

Example 724

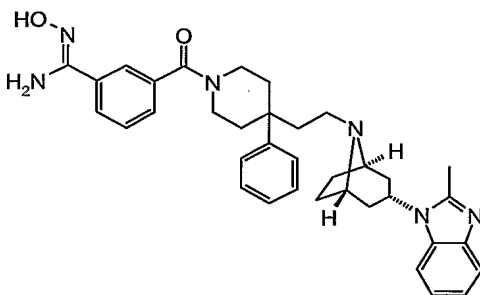
endo 2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[3-(2H-tetraazol-5-yl)benzoyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



5 To a solution of title compound from example 723 (40 mg, 0.0717 mmol) in toluene (4 ml)) was added trimethylsilylazide (24.77 mg, 0.215 mmol) and dibutyltin oxide (16.18 mg, 0.065 mmol), the mixture was heated to reflux for 15 h, diluted with dichloromethane (20 ml), dried over sodium sulfate and concentrated. The crude product was purified by column
10 chromatography on silica gel, eluting with a gradient of 5-20% methanol in dichloromethane to afford endo 2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[3-(2H-tetraazol-5-yl)benzoyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1] oct-3-yl]-1H-benzimidazole as a solid (36 mg, 84%). ¹H-NMR (300 MHz, MeOD) δ 8.18 (d, 1H, J=7.8 Hz), 8.11 (s, 1H), 7.61-7.55 (m, 2H), 7.50-7.42 (m, 6H), 7.33-7.22 (m, 3H), 5.01-4.82 (m, 1H), 4.35-4.20 (br m, 1H), 3.85-3.80 (br m, 2H), 3.70-3.65 (br m, 1H), 3.32-3.27 (m, 2H), 2.73-2.63 (m, 2H), 2.57 (s, 3H), 2.53-2.50 (m, 1H), 2.48-2.37 (m, 1H), 2.31-1.86 (m, 12H). HRMS *m/z* (M+H) 601.3211 Cal., 601.387 Obs.

Example 725

endo N'-hydroxy-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-yl)carbonyl]benzenecarboximidamide



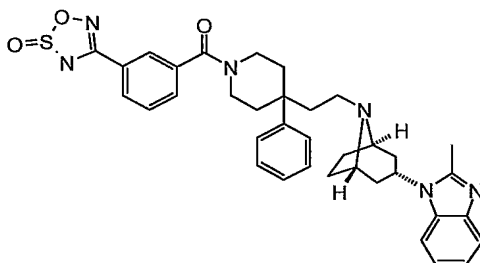
5

To a suspension of hydroxylamine hydrochloride (1.706 g, 24.55 mmol) in a 9:1 mixture of methanol-water (8 ml) was added triethylamine (3.42 ml, 24.55 mmol), followed by the title compound from example 723 (2.74 g, 4.91 mmol). After heating to reflux for 1h, a solid which precipitated was collected by filtration to afford endo N'-hydroxy-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-yl)carbonyl]benzenecarboximidamide (1.49 g, 51.3%). ¹H NMR (300 MHz, DMSO-d₆) δ 9.71 (s, 1H), 7.75 (d, 1H, J= 7.6 Hz), 7.66 (s, 1H), 7.51-7.35 (m, 8H), 7.26-7.21 (m, 1H), 7.15-7.07 (m, 2H), 5.88 (s, 2H), 4.57-4.51 (br m, 1H), 3.91-3.83 (br m, 1H), 3.50-3.40 (m, 2H), 3.26-3.16 (br m, 3H), 2.44 (s, 3H), 2.38-2.32 (m, 2H), 2.13-2.09 (br m, 2H), 1.85-1.73 (m, 10H), 1.61-1.58 (br m, 2H). HRMS *m/z* (M+H) 591.3448 Cal., 591.3458 Obs.

15

Example 726

endo 2-methyl-1-[(1R,5S)-8-(2-{1-[3-(2-oxido-3H-1,2,3, 5-oxathiadiazol-4-yl)benzoyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



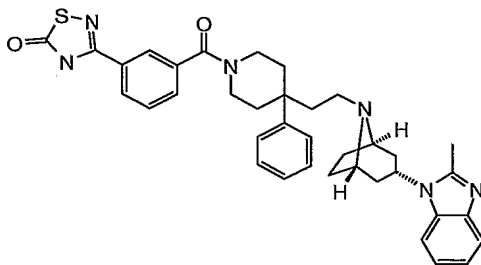
5

The title compound was prepared (based on procedure from Yasuhisa Kohara, Keiji Kubo, Eiko Imamiya, Takeo Wada, Yoshiyuki Inada and Takehiko Naka, "Synthesis and Angiotensin II Receptor Antagonistic Activities of Benzimidazole Derivatives Bearing Acidic Heterocycles as Novel Tetrazole Bioisosteres." *J. Med. Chem.*, 39, 5228-5235 (1996)) from the product obtained in example 725 (200 mg, 0.339 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 2.5-15% methanol in dichloromethane to afford endo 2-methyl-1-[(1R,5S)-8-(2-{1-[3-(2-oxido-3H-1,2,3,5-oxathiadiazol-4-yl)benzoyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole as a white solid (41 mg, 19 %). ¹H-NMR (300 MHz, MeOH-d₄) δ 8.02 (d, 1H, J=7.3 Hz), 7.96 (s, 1H), 7.60-7.43 (m, 8H), 7.34-7.23 (m, 3H), 4.98-4.89 (m, 1H), 4.30-4.24 (br m, 1H), 3.87-3.84 (br m, 2H), 3.71-3.63 (br m, 1H), 3.36-3.25 (m, 3H), 2.73-2.40 (m, 5H), 2.61 (s, 3H), 2.31-1.92 (m, 9H). HRMS *m/z* (M+H) 637.2961 Cal., 637.2974 Obs.

20

Example 727

endo 3-{3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-
azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}-1,2,4-
thiadiazol-5(4H)-one

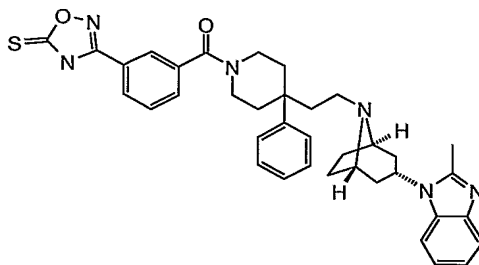


The title compound in example 727 was prepared (based on procedure from Yasuhisa Kohara, Keiji Kubo, Eiko Imamiya, Takeo Wada, Yoshiyuki Inada and Takehiko Naka, "Synthesis and Angiotensin II Receptor Antagonistic Activities of Benzimidazole Derivatives Bearing Acidic Heterocycles as Novel Tetrazole Bioisosteres." *J. Med. Chem.*, 39, 5228-5235 (1996)) from the product obtained in example 725 (300 mg, 0.5078 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 5-10% methanol in dichloromethane to afford endo 3-{3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}-1,2,4-thiadiazol-5(4H)-one as a thick oil (57 mg, 17.7%). ¹H-NMR (300 MHz, MeOH-d₄) δ 8.06 (d, 1H, J=7.6 Hz), 8.00 (s, 1H), 7.82 (br s, 2H), 7.61-7.54 (m, 3H), 7.51-7.46 (m, 3H), 7.30-7.21 (m, 3H), 4.89-4.80 (m, 1H), 4.30-4.18 (br m, 1H), 3.75-3.52 (br m, 3H), 3.36-3.32 (m, 3H), 2.58-2.45 (m, 1H), 2.55 (s, 3H), 2.40-1.81 (m, 14H). HRMS *m/z* (M+H)⁺ 633.3011 Cal., 633.3013 Obs.

Example 728

endo 3-{3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-
azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}-1,2,4-
oxadiazole-5(4H)-thione

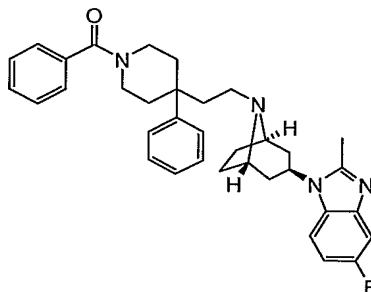
497



The title compound was prepared (based on procedure from Yasuhisa Kohara, Keiji Kubo, Eiko Imamiya, Takeo Wada, Yoshiyuki Inada and Takehiko Naka, "Synthesis and Angiotensin II Receptor Antagonistic Activities of Benzimidazole Derivatives Bearing Acidic Heterocycles as Novel Tetrazole Bioisosteres." *J. Med. Chem.*, 39, 5228-5235 (1996)) from the product obtained in example 725 (300 mg, 0.5078 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 5-10% methanol in dichloromethane to afford endo 3-{3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}-1,2,4-oxadiazole-5(4H)-thione as a white solid (32 mg, 10%). ¹H-NMR (300 MHz, MeOH-d₄) δ 8.03 (d, 1H, J=7.6 Hz), 7.96 (s, 1H), 7.59-7.42 (m, 8H), 7.39-7.20 (m, 3H), 4.97-4.88 (m, 1H), 4.25-4.18 (br m, 1H), 3.73-3.25 (br m, 6H), 2.68-2.60 (m, 1H), 2.57 (s, 3H), 2.57-1.83 (m, 914H). HRMS *m/z* (M+H)⁺ 633.3011 Cal., 633.2999 Obs.

Example 729

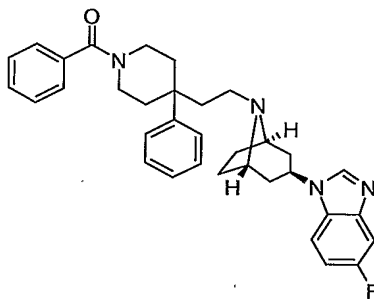
exo 1-{(1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-5-fluoro-2-methyl-1H-benzimidazole



The title compound was prepared from exo 5-fluoro-2-methyl-1-
{(1R,5S)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-
benzimidazole (200 mg, 0.448 mmol), which was obtained using analogous
chemistry to that described in the synthesis of exo1-(8-azabicyclo[3.2.1]oct-3-
yl)-2-methyl-1H-benzimidazole as described elsewhere in this application, and
5 benzoyl chloride (75.6 mg, 0.54 mmol). Products were purified by Plate
Purification Method A to afford exo 1-{(1R,5S)-8-[2-(1-benzoyl-4-
phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-5-fluoro-2-methyl-1H-
benzimidazole as an oil (1 mg, 0.4%). ES-LC/MS (CLND) m/z 551 (M+H)⁺.

Example 730

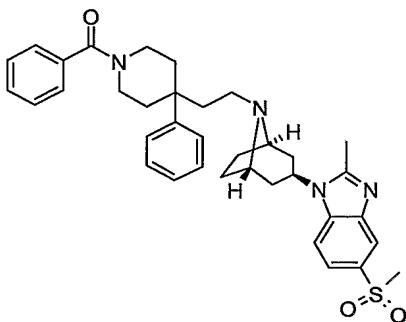
exo 1-{(1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-
azabicyclo[3.2.1]oct-3-yl}-5-fluoro-1H-benzimidazole



The title compound was prepared as described in example 729 from
exo 5-fluoro-1-{(1R,5S)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-
azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole (100 mg, 0.231 mmol), which
was obtained using analogous chemistry to that described in the synthesis of
exo1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as described
elsewhere in this application, and benzoyl chloride (35.7 mg, 0.254 mmol)
and purified by Plate Purification Method A to afford exo 1-{(1R,5S)-8-[2-(1-
benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-5-fluoro-1H-
benzimidazole as an oil (1 mg, 0.8%). ES-LCMS (CLND) m/z 537 (M+H)⁺.

Example 731

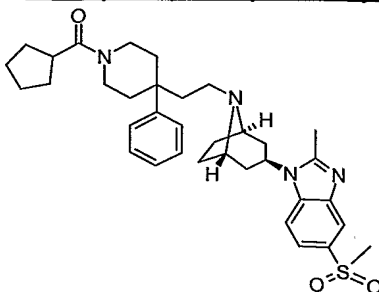
exo 1-((1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-5-(methylsulfonyl)-1H-benzimidazole



5 The title compound was prepared from exo 2-methyl-5-(methylsulfonyl)-1-((1R,5S)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole (100 mg, 0.197 mmol), which was obtained using analogous chemistry to that described in the synthesis of
10 exo-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as described elsewhere in this application, and benzoyl chloride (41.5 mg, 0.296 mmol), purified by Plate Purification Method A to afford exo 1-((1R,5S)-8-[2-(1-benzoyl-4-phenyl piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-5-(methylsulfonyl)-1H-benzimidazole as an oil (1 mg, 0.8%). ES-LCMS (CLND) m/z 611 (M+H)⁺.

Example 732

exo 1-((1R,5S)-8-[2-[1-(cyclopentylcarbonyl)-4-phenylpiperidin-4-yl]ethyl]-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-5-(methylsulfonyl)-1H-benzimidazole

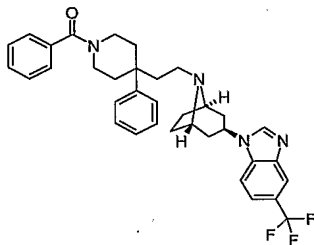


20 The title compound was prepared from exo 2-methyl-5-(methylsulfonyl)-1-((1R,5S)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-

azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole (100 mg, 0.197 mmol), which was obtained using analogous chemistry to that described in the synthesis of exo-1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as described elsewhere in this application, and cyclopentane carbonyl chloride (39.2 mg, 0.296 mmol) and purified by Plate Purification Method A to afford exo 1-
5 ((1R,5S)-8-{2-[1-(cyclopentyl carbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo [3.2.1]oct-3-yl)-2-methyl-5-(methylsulfonyl)-1H-benzimidazole as an oil (0.9 mg, 0.75%). ES-LCMS (CLND) m/z 603 (M+H)⁺.

Example 733

exo 1-((1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl)-5-(trifluoromethyl)-1H-benzimidazole

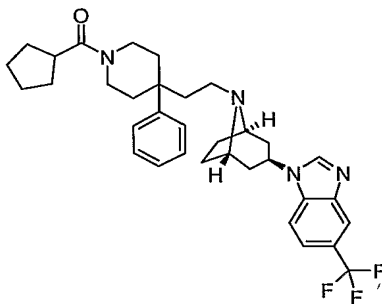


The title compound was prepared from exo 1-((1R,5S)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl)-5-(trifluoromethyl)-1H-benzimidazole (110 mg, 0.228 mmol), which was obtained using analogous chemistry to that described in the synthesis of exo 1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as described elsewhere in this application, and benzoyl chloride (48.1 mg, 0.342 mmol). The crude was purified by Plate
15 Purification Method A to afford exo 1-((1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl)-5-(trifluoromethyl)-1H-benzimidazole as an oil (3.4 mg, 2.5%). ES-LCMS (CLND) m/z 587 (M+H)⁺.

501

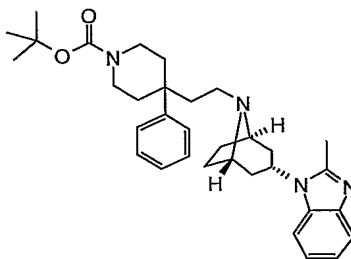
Example 734

exo 1-((1R,5S)-8-{2-[1-(cyclopentylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-5-(trifluoromethyl)-1H-benzimidazole



5 The title compound was prepared from exo 1-((1R,5S)-8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl)-5-(trifluoromethyl)-1H-benzimidazole (110 mg, 0.228 mmol), which was obtained using analogous chemistry to that described in the synthesis of exo 1-(8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as described elsewhere in this application, and
10 cyclopentane carbonyl chloride (48.1 mg, 0.342 mmol). The crude was purified by Plate Purification Method A to afford exo 1-((1R,5S)-8-[2-[1-(cyclopentylcarbonyl)-4-phenylpiperidin-4-yl]ethyl]-8-azabicyclo[3.2.1]oct-3-yl)-5-(trifluoromethyl)-1H-benzimidazole as an oil (4.8 mg, 3.6%). ES-LCMS (CLND) m/z 579 (M+H)⁺.

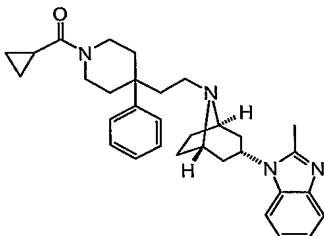
15 Examples 735-737 were synthesized by deprotecting the Boc-protected intermediate depicted below and acylation via CDI method, described in example 723.



20

Example 735

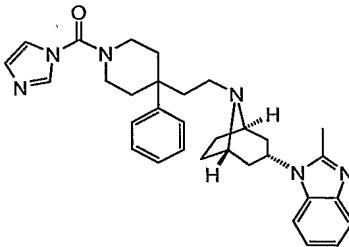
endo 1-((1R,5S)-8-{2-[1-(cyclopropylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



5 The title compound was prepared as described in example 723 from cyclopropane carboxylic acid (9.3 mg, 0.108 mmol) and purified by column chromatography on silica gel, eluting with a gradient of 2-10% methanol in dichloromethane to afford endo 1-((1R,5S)-8-{2-[1-(cyclopropylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-
10 benzimidazole as a colorless oil (41 mg, 77%). ¹H-NMR (300 MHz, DMSO-d₆) δ 7.50 (dd, 1H, J=2.8, 2.1 Hz), 7.43-7.35 (m, 4H), 7.25-7.02 (m, 4H), 4.57-4.49 (m, 1H), 3.86-3.76 (m, 2H), 3.38-3.17 (m, 6H), 2.49 (s, 3H), 2.42-2.31 (m, 2H), 2.31-1.77 (m, 10H), 1.65-1.58 (m, 2H), 0.80-0.62 (m, 5H). HRMS m/z (M+H) 497.3280 Cal., 497.3274 Obs.

Example 736

endo 1-((1R,5S)-8-{2-[1-(1H-imidazol-1-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

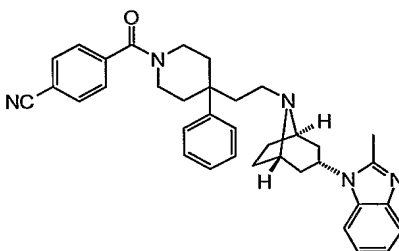


20 The title compound was prepared as described in example 723 from 2-thiophene carboxylic acid (13.84 mg, 0.108 mmol). The reaction mixture was stirred at room temperature overnight. The crude product was purified by column chromatography on silica gel, eluting with a gradient of 2-10%

methanol in dichloromethene to afford endo 1-((1R,5S)-8-{2-[1-(1H-imidazol-1-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole as a colorless oil (28.6 mg, 49.4%). ¹H-NMR (300 MHz, CDCl₃) δ 7.86 (s, 1H), 7.71-7.67 (m, 1H), 7.45-7.39 (m, 2H), 7.33-7.24 (m, 4H), 7.22-7.11 (m, 4H), 4.67-4.62 (m, 1H), 3.91-3.80 (m, 2H), 3.40-3.22 (m, 4H), 2.60 (s, 3H), 2.50-2.34 (m, 4H), 2.10-1.96 (m, 10H), 1.69-1.63 (m, 2H). HRMS *m/z* (M+H) 523.3185 Cal., 523.3190 Obs.

Example 737

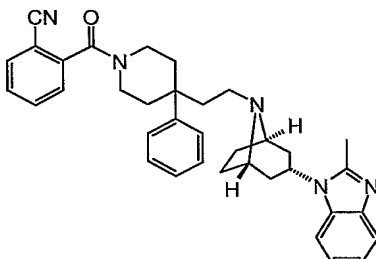
endo 4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzonitrile



The title compound was prepared as described in example 723 from 4-cyanobenzoic acid (47.53 mg, 0.322 mmol). The reaction mixture was stirred at room temperature overnight. The crude was purified by column chromatography on silica gel, eluting with 3% methanol in dichloromethene to afford endo 4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzonitrile as a colorless oil (58 mg, 32%). ¹H-NMR (300 MHz, CDCl₃) δ 7.74-7.67 (m, 3H), 7.51-7.26 (m, 8H), 7.22-7.13 (m, 2H), 4.65-4.59 (m, 1H), 4.25-4.20 (br m, 1H), 3.55-3.25 (m, 4H), 2.58 (s, 3H), 2.45-2.33 (br m, 3H), 2.21-2.17 (br m, 1H), 1.96-1.80 (m, 11H), 1.76-1.62 (m, 2H). HRMS *m/z* (M+H) 558.3318 Cal., 558.3237 Obs.

Example 738

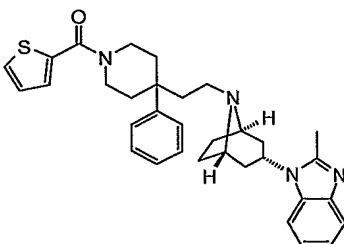
endo 2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzonitrile



The title compound was prepared as described in example 710 by coupling 2-carboxybenzonitrile (36.5 mg, 0.247 mmol) *via* HATU (method M) and purified by column chromatography on silica gel, eluting with 5% methanol in dichloromethane to afford endo 2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzonitrile as a rigid foam (66 mg, 48%). ¹H NMR (300 MHz, CDCl₃) δ 7.75-7.65 (m, 3H), 7.56-7.15 (m, 10H), 4.69-4.63 (m, 1H), 4.32-4.27 (br m, 1H), 3.45-3.35 (m, 4H), 2.58 (s, 3H), 2.46-2.38 (m, 3H), 2.20-2.19 (br m, 2H), 2.17-1.82 (m, 10H), 1.75-1.62 (m, 2H). HRMS *m/z* (M+H) 558.3233 Cal., 558.3226 Obs.

Example 739

endo 2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(thien-2-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole

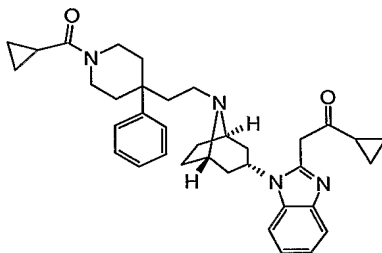


The title compound was prepared from 2-thiophene carboxylic acid (24 mg, 0.186 mmol) using EDCI-HOBT (method P) and purified by column chromatography on silica gel, eluting with 5% methanol in dichloromethane to afford endo 2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(thien-2-

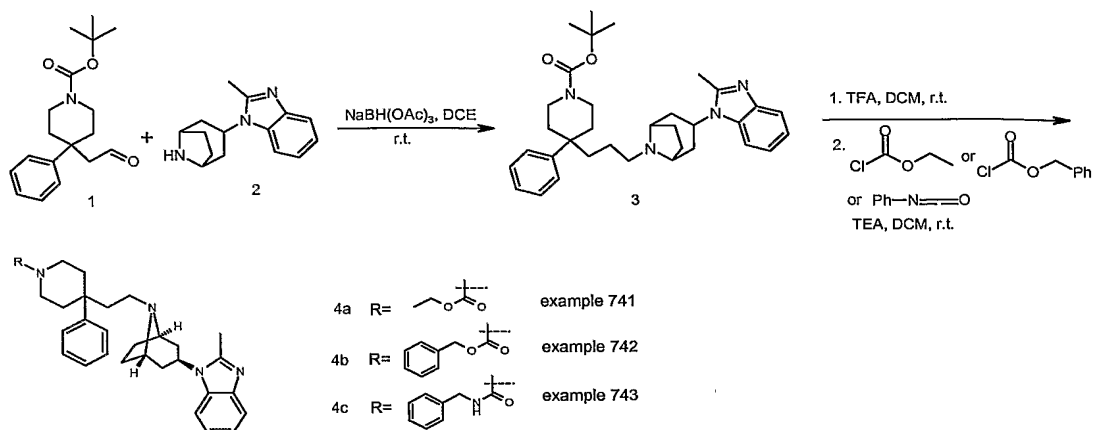
ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole as a colorless oil (14 mg, 14%). ¹H-NMR (300 MHz, CDCl₃) δ 7.68-7.67 (d, 1H, J=6.9 Hz), 7.46-7.15 (m, 10H), 7.13-7.04 (m, 1H), 4.66-4.60 (m, 1H), 4.16-4.00 (br m, 2H), 3.50-3.40 (m, 2H), 3.30-3.25 (br m, 2H), 2.58 (s, 3H), 2.42-2.28 (m, 4H), 2.11-1.98 (m, 10H), 1.72-1.63 (m, 2H). HRMS *m/z* (M+H) 539.2845 Cal., 539.2859 Obs.

Example 740

endo 1-cyclopropyl-2-[1-(8-{2-[1-(cyclopropylcarbonyl)-4-phenylpiperidine-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazol-2-yl]ethanone



The title compound was prepared as described in Example 3, from cyclopropane carbonyl chloride (12.36 mg, 0.118 mmol), *via* acid chloride Method Q, to afford endo 1-cyclopropyl-2-[1-(8-{2-[1-(cyclopropylcarbonyl)-4-phenylpiperidine-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazol-2-yl]ethanone as an off-white foam (26 mg, 43%). ¹H-NMR (300 MHz, CDCl₃) δ 7.76-7.72 (m, 1H), 7.40-7.34 (m, 5H), 7.33-7.18 (m, 3H), 4.56-4.54 (m, 1H), 4.23-4.19 (m, 2H), 4.15-3.94 (m, 2H), 3.48-3.40 (m, 1H), 3.38-3.26 (m, 3H), 2.42-2.13 (m, 5H), 1.94-1.74 (m, 11H), 1.70-1.62 (m, 2H), 1.13-1.03 (m, 2H), 1.02-0.95 (m, 4H), 0.88-0.75 (m, 2H). HRMS *m/z* (M+H) 565.3543 Cal., 565.3541 Obs.

Synthesis of carbamates, examples 741-743Synthesis of 3 of the above scheme:

To a solution of **1** (0.3 g, 1 mmol) in dichloroethane (15 mL), amine **2** (0.032g, 0.148 mmol) was added $\text{NaBH}(\text{OAc})_3$ (0.424 g, 2 mmol). The mixture was stirred at r.t. overnight, and then quenched with saturated sodium bicarbonate solution, extracted with methylene chloride, dried over sodium sulfate, filtered and concentrated. Purification by chromatotron with 5% MeOH and 0.5% ammonium hydroxide in methylene chloride gave 0.267 g as white solid. ^1H NMR (400 MHz, CDCl_3 , ppm) δ 7.62-7.59 (1H, m), 7.36-7.28 (5H, m), 7.20-7.18 (1H, m), 7.14-7.10 (2H, m), 4.43-4.34 (1H, m), 3.68-3.60 (2H, broad), 3.24 (2H, broad s), 3.18 (2H, td, $J=9.3$ Hz, 2.5 Hz), 2.48 (3H, s), 2.39 (2H, broad t, $J=11.9$ Hz), 2.20-2.18 (4H, broad), 1.88-1.74 (6H, broad m), 2.10-1.97 (3H, m), 1.79-1.65 (6H, m), 1.55 (2H, d, $J=8.1$ Hz), 1.47 (2H, dd, $J=5.2$ Hz, 3.5 Hz), 1.40 (9H, s). ^{13}C NMR (400 MHz, CDCl_3 , ppm) δ 155.20, 151.20, 144.83, 143.19, 133.75, 128.82, 126.82, 126.37, 121.96, 121.69, 119.42, 111.49, 79.53, 58.71, 48.38, 46.41, 41.38, 40.66, 39.43, 35.75, 34.42, 28.69, 26.88, 14.96. LRMS: calcd. for $\text{C}_{34}\text{H}_{45}\text{Cl}_2\text{N}_4\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 611.3.

Synthesis of 4a-4c of the above scheme:

Deprotection of Boc with 25% TFA in dichloromethane at r.t. was followed by quenching with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried, filtered and

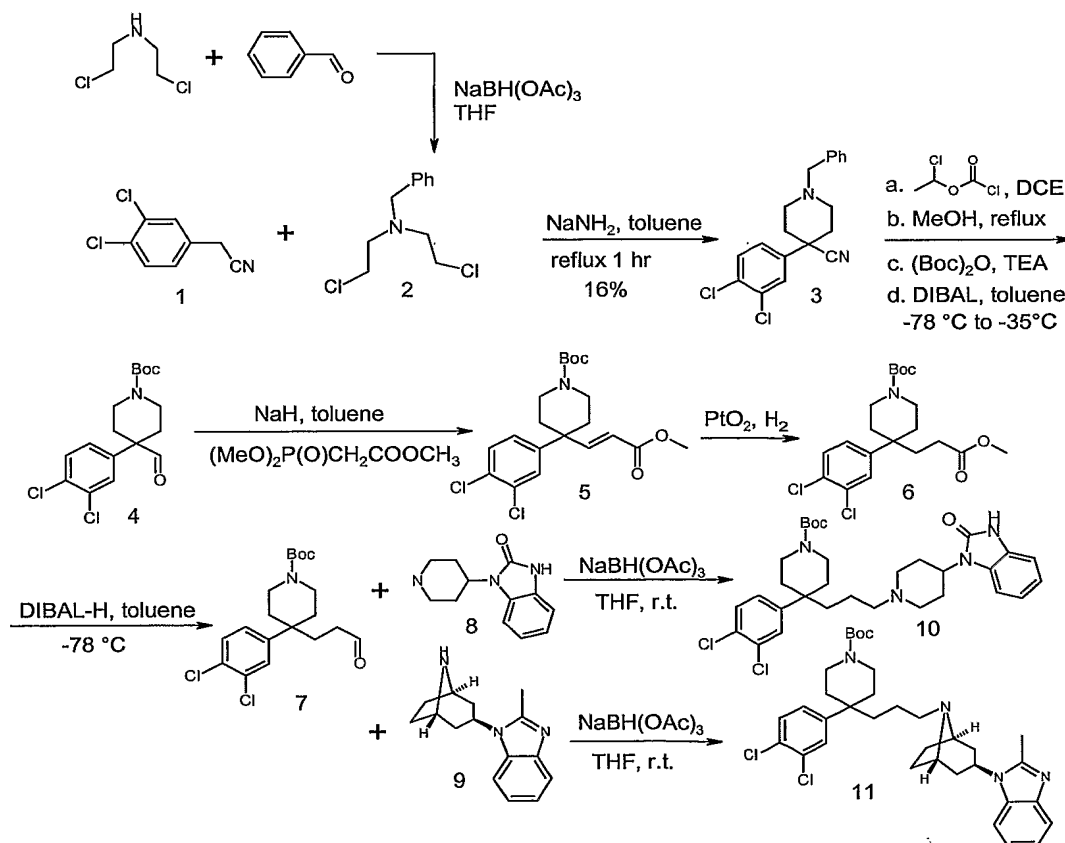
concentrated. 1 eq. of chloroformates or phenyl isocyanate and 3 eq. triethyl amine were used at r.t. until the reactions were complete by LC-MS. The final products were purified by PHPLC.

Example 741: 1.7 mg. HRMS: calcd. for $C_{31}H_{41}N_4O_2$ (M+H)⁺ 501.3230, found: 501.3205.

Example 742: 1.3 mg. HRMS: calcd. for $C_{36}H_{43}N_4O_2$ (M+H)⁺ 548.3389, found: 548.3405.

Example 743: 1.0 mg. HRMS: calcd. for $C_{35}H_{42}N_5O$ (M+H)⁺ 563.3386, found: 563.3379.

The synthesis of analogues with C3-linker dichloro analogues



Synthesis of 2 of the above scheme:

To a suspension of bis(2-chloroethyl)amine hydrochloride (22.48 g, 125.9 mmol) in dichloroethane (300 mL), benzaldehyde (14.1 mL, 138.5

mmol), triethyl amine (43.8 mL, 314.9 mmol) and NaBH(OAc)₃ were added sequentially. The cloudy content was stirred at r.t. overnight. It was then quenched with saturated sodium bicarbonate solution, extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated to give 35.7 g product as oil. ¹H NMR (400 MHz, CDCl₃) δ[ppm]: 7.33-7.31 (5H, m), 3.73 (2H, s), 3.49 (4H, t, J=7.1 Hz), 2.92 (4H, t, J=7.2 Hz). ¹³CNMR (400 MHz, CDCl₃) δ[ppm]: 139.06, 128.83, 128.69, 127.87, 127.62, 127.24, 59.43, 56.59, 42.43.

Synthesis of 3 of the above scheme:

To a solution of 1 (1.18 g, 6.32 mmol) in toluene (50 mL), NaNH₂ (1.48 g, 50% in toluene, 18.96 mmol) was added at r.t. (the content turned red upon the addition of sodium amide). The mixture was then heated to reflux for 1 hour. The reaction was quenched with HCl (0.1N, 50 mL). The content pH was adjusted to ~11 with NaOH (50% aqous solution). The organic layer was separated. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was dried (Na₂SO₄), filtered and concentrated. The residue was purified by flash column chromatography with hexane/ethyl acetate (8/1 to 4/1) afforded 0.38 g product as red oil (17%). ¹H NMR (400 MHz, CDCl₃) δ[ppm]: 7.58 (1H, d, J=2 Hz), 7.49 (1H, d, J=14.1 Hz), 7.45-7.28 (6H, m), 3.59 (2H, s), 2.99 (2H, d, J=11.8 Hz), 2.51-2.48 (2H, broad m), 2.07-2.05 (4H, broad). ¹³CNMR (400 MHz, CDCl₃) δ[ppm]: 140.75, 138.18, 133.49, 131.16, 129.29, 128.62, 128.47, 128.15, 127.54, 125.40, 121.47, 63.07, 50.75, 42.62, 36.78. LRMS: calcd. for C₁₉H₁₈Cl₂N₂ (M⁺) 344.1, found 344.3.

Synthesis of 4 of the above scheme:

To a solution of 3 (3.28 g, 9.53 mmol) in dichloroethane (200 mL), 1-chloroethyl chloroformate (1.54 mL, 14.30 mmol) was added at 0°C and stirred for 15 mins. It was then heated to reflux for 1 hr. After cooling to the r.t., the dichloroethane was removed under reduced pressure. The residue was dissolved in methanol and heated to reflux for 20 mins (reaction was complete by GC-MS). The methanol was removed under reduced pressure. After redissolving the residue in THF (150 mL), (Boc)₂O (3.12 g, 14.3 mmol)

and triethyl amine (4.0 mL, 28.60 mmol) were added. The content was stirred at r.t. overnight. Ethyl acetate was added. The organic layer was washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), filtered and concentrated. Flash column chromatography with hexane/EtOAc (8/1 to 6/1) afforded 0.677 g product as yellow solid (20% yield) and another impure fraction (0.894 g, ~85% purity). ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 7.50 (1H, d, $J=2.2$ Hz), 7.43 (1H, d, $J=8.7$ Hz), 7.27 (1H, dd, $J=8.6$ Hz, 2.2 Hz), 4.24 (2H, broad s), 3.12 (2H, broad s), 2.03-1.98 (2H, m), 1.88-1.80 (2H, m), 1.43 (9H, s). ^{13}C NMR (400 MHz, CDCl_3) δ [ppm]: 154.45, 140.09, 133.57, 132.87, 131.28, 128.01, 125.31, 120.68, 80.51, 42.72, 41.31, 36.30, 28.59. LRMS: calcd. for $\text{C}_{17}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_2$ (M^+) 354.1 found 354.2.

To a solution of the product from the last step (0.677 g, 1.91 mmol) in toluene (30 mL), DIBAL-H (5.7 mL, 1M in toluene) was added at -78°C . The content was warmed to -35°C over 3.5 hrs period. The reaction was completed (monitored by GC-MS) and then quenched with saturated ammonium chloride solution (30 mL). The content was extracted with ethyl acetate (GC-MS indicated that incomplete quenching might lead to the cleavage of Boc protecting group. MeOH might be a better choice of quenching reagent). So the content was retreated with $(\text{Boc})_2\text{O}$ (2 eq.) and triethyl amine (2 eq.) for 2 hrs. The organic layer was washed with NaOH (0.1N), separated, dried (Na_2SO_4), filtered and concentrated. Flash column chromatography with hexane/ethyl acetate (8/1) afforded 0.14 g (21% yield). ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 9.38 (1H, s), 7.40 (1H, d, $J=17.4$ Hz), 7.36 (1H, d, $J=2.2$ Hz), 7.10 (1H, $J=2.1$ Hz), 3.86 (2H, broad s), 3.08 (2H, broad), 2.34 (2H, d, $J=13.7$ Hz), 1.92 (2H, broad), 1.44 (9H, s). LRMS calcd. for $\text{C}_{12}\text{H}_{13}\text{Cl}_2\text{NO}$ (M-Boc+H^+) 257.0, found 257.1.

Synthesis of 5 of the above scheme:

To a suspension of NaH (0.025 g, 60% in mineral oil, 0.627 mmol) in toluene, trimethyl phosphonoacetate (0.1 mL, 0.627 mmol) was added. The content was stirred at r.t. for 1 hr before 4 (0.14 g, 0.392 mmol) in toluene (2 mL) was added (in case of a large scale reaction, an ice bath is necessary to

control the reaction). The content was stirred at r.t. overnight during which it turned cloudy. The reaction was quenched with water. The content was extracted with ethyl acetate. The combined organic layer was dried (Na_2SO_4), filtered and concentrated. ^1H NMR (400 MHz, CDCl_3) δ [ppm]: (crude) 7.40 (1H, d, $J=8.6$ Hz), 7.33 (1H, $J=2$ Hz), 7.10 (1H, dd, $J=8.4$ Hz, 2.0 Hz), 6.90 (1H, $J=16.1$ Hz), 5.67 (1H, $J=16.1$ Hz), 3.71 (3H, s), 3.52-3.36 (4H, m), 2.08-1.96 (4H, m), 1.44 (9H, s).

Synthesis of 6 of the above scheme:

To a solution of the residue in EtOH (15 mL), PtO_2 was added. The content was stirred under 1 atm H_2 for 3 hrs (the reaction was complete by GC-MS). The content was filtered through celite and concentrated. Flash column chromatography with hexane/ethyl acetate (4/1) afforded 0.123 g (76% yield) product as oil. ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 7.42 (1H, d, $J=8.4$ Hz), 7.32 (1H, $J=2.1$ Hz), 7.10 (1H, dd, $J=8.6$ Hz, 2.2 Hz), 3.64 (2H, broad), 3.57 (3H, s), 3.11 (2H, t, $J=10$ Hz), 2.07-1.89 (6H, m), 1.72-1.67 (2H, m), 1.43 (9H, s).

Synthesis of 7 of the above scheme:

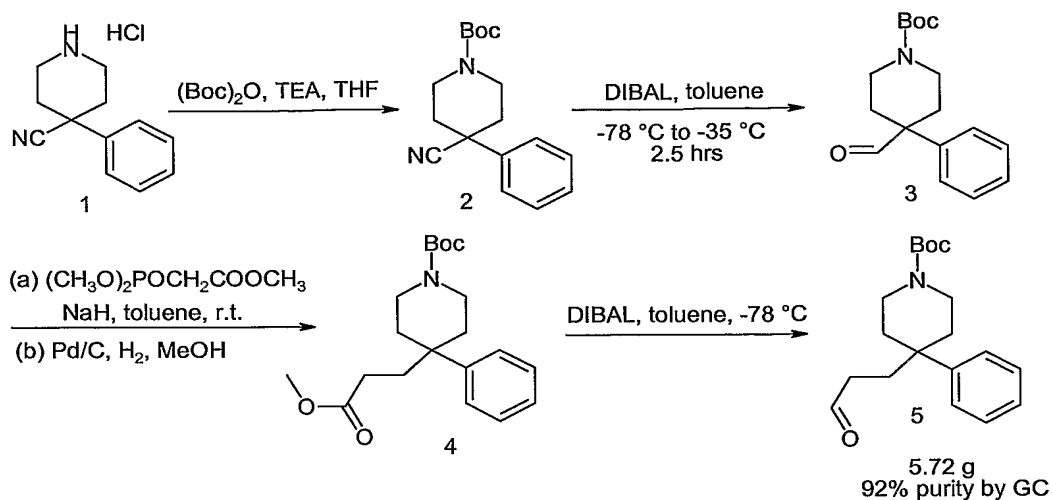
DIBAL-H (0.593 mL, 1M in toluene, 0.593 mmol) was cooled to -78°C and added into a solution of **6** (0.123 g, 0.296 mmol) in toluene (15 mL) (also cooled to -78°C with a dry ice-acetone bath, necessary to prevent overreduction) dropwise (to keep the internal temperature as low as possible). The content was stirred at -78°C for 2.5 hrs and the reaction was quenched with a cooled MeOH (-78°C) dropwise (the addition needs to be slow to keep the internal temperature low and prevent overreduction). After the addition completed, the content was warmed to r.t. and filtered through celite. The filtrate was washed with brine. The aqueous layer was extracted with ethyl acetate. The combined organic layer was dried with Na_2SO_4 , filtered and concentrated. ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 9.59 (1H, s), 7.41 (1H, d, $J=8.4$ Hz), 7.37 (1H, d, $J=3.8$ Hz), 7.31 (1H, dd, $J=8.3$ Hz, 2.2 Hz), 3.66-3.63 (2H, m), 3.12-3.06 (2H, m), 2.13-2.02 (4H, m), 1.89-1.85 (2H, m), 1.77-1.64 (2H, m), 1.44 (9H, s).

Synthesis of 10 of the above scheme:

To a solution of 7 (1/2 the residue from the last step, ~0.148 mmol) in THF (15 mL), amine 8 (0.032g, 0.148 mmol) was added. The content was stirred at r.t. for 10 mins before NaBH(OAc)₃ (0.094 g, 0.444 mmol) was added. It was stirred at r.t. overnight, and then quenched with saturated sodium bicarbonate solution, extracted with methylene chloride, dried over sodium sulfate, filtered and concentrated. Prep. TLC purification with 5% MeOH and 0.5% ammonium hydroxide in methylene chloride gave 9 mg product. ¹H NMR (400 MHz, CDCl₃) δ[ppm]: 9.13 (1H, s), 7.40 (1H, d, J=8.5 Hz), 7.34 (1H, d, J=1.9 Hz), 7.07 (1H, dd, J=8.4 Hz, 1.9 Hz), 4.32 (1H, broad s), 3.63 (2H, m), 3.12 (2H, broad t, J=10.2 Hz), 2.92 (2H, broad s), 2.42 (1H, broad s), 2.22 (2H, broad s), 2.10-1.97 (3H, m), 1.79-1.65 (6H, m), 1.58 (2H, broad s), 1.43 (9H, s), 1.12-1.08 (2H, broad). HRMS: calcd. for C₃₁H₄₁Cl₂N₄O₃ (M+H)⁺ 587.2556, found 587.2565.

Synthesis of 11 of the above scheme:

Following the route described towards 10, 43 mg of product 11 was synthesized. ¹H NMR (400 MHz, CDCl₃) δ[ppm]: 7.66-7.63 (1H, m), 7.56 (1H, broad s), 7.40-7.36 (2H, m), 7.20-7.13 (3H, m), 4.52-4.43 (1H, m), 3.63 (2H, m), 3.26 (2H, broad s), 3.18 (2H, td, J=9.2 Hz, 2.8 Hz), 2.58-2.48 (5H, broad), 2.33-2.28 (2H, m), 2.07-2.00 (4H, m), 1.76-1.60 (8H, m), 1.44 (9H, s), 1.19 (2H, broad s). LRMS: calcd. for C₃₄H₄₅Cl₂N₄O₂ (M+H)⁺ 611.3, found 611.0.

The synthesis of analogues with C3-linker- unsubstituted scaffoldSynthesis of 2 of the above scheme:

To a suspension of **1** (22 g, 98.8 mmol) in THF (300 mL), TEA (45 mL,
 326 mmol) and (Boc)₂O (24 g, 110 mmol) were added and the content was
 stirred at r.t. overnight, followed by addition of HCl (250 mL, 0.1 N) and the
 mixture was extracted with ethyl acetate. The organic layer was combined,
 dried over Na₂SO₄, filtered and concentrated to give 26.2 g product as white
 crystalline solid (93% yield). ¹H NMR (400 MHz, CDCl₃) δ[ppm]: 7.46-7.25
 (5H, m), 4.26 (2H, brs), 3.18 (2H, brs), 2.07 (2H, d, J=13.5Hz), 1.93 (3H, t,
 J=9.4Hz), 1.47 (9H, s). ¹³CNMR (400 MHz, CDCl₃) δ[ppm]: 154.67, 139.88,
 129.54, 129.38, 128.57, 125.77, 121.60, 80.39, 43.20, 41.52, 36.48, 28.65.
 LRMS: m/z calcd. for C₁₇H₂₂N₂O₂ (M⁺) 286.17, found 286.2.

Synthesis of 3 of the above scheme:

DIBAL-H (60 mL, 1M in hexane, 60 mmol) was added to a solution of **2**
 (8.0 g, 28.0 mmol) in toluene (200 mL) at -78°C with a dry-ice acetone bath.
 The content was warmed to -35°C over about 2 hrs and stirred at -35°C for
 another hour. The reaction was quenched with saturated ammonium chloride
 (100 mL), filtered through celite. The organic layer was separated, dried
 (Na₂SO₄), filtered and concentrated to afford 6.95 g product as light yellow oil
 (86% yield). ¹H NMR (400 MHz, CDCl₃) δ[ppm]: 9.40 (1H, s), 7.45-7.25 (5H,
 m), 3.85 (2H, brs), 3.10 (2H, br), 2.36 (2H, d, J=13.6 Hz), 1.98 (2H, br), 1.44

(9H, s). ^{13}C NMR (400 MHz, CDCl_3) δ [ppm]: 201.18, 154.96, 138.34, 129.40, 128.02, 127.16, 79.93, 53.26, 40.88, 30.77, 28.64. LRMS: m/z calcd. for $\text{C}_{17}\text{H}_{23}\text{NO}_3$ 289.2, found 289.2 (M^+).

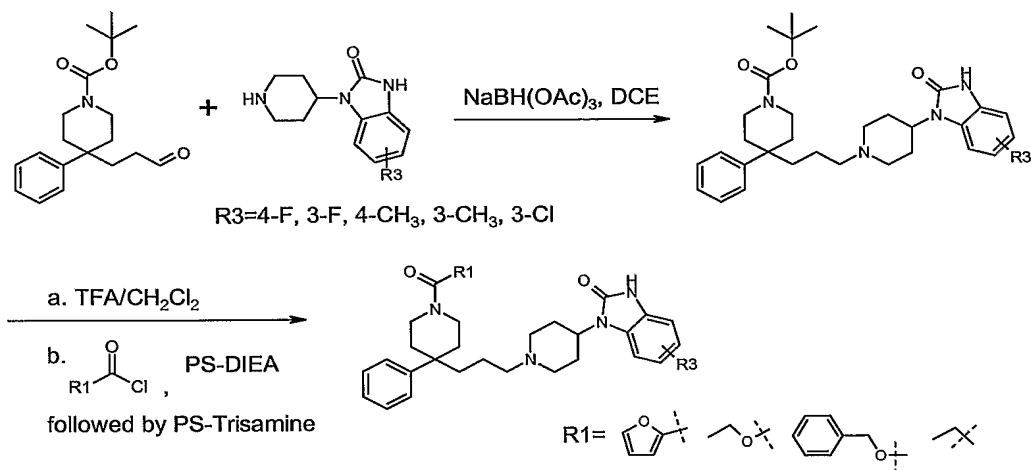
Synthesis of 4 of the above scheme:

5 To a suspension of NaH (1.15 g, 60% in mineral oil, 28.86 mmol) in toluene (100 mL) at 0°C, trimethyl phosphonoacetate (4.28 mL, 26.45 mmol) was added dropwise and the content was warmed up to r.t. and stirred for 50 mins. A solution of 3 (6.95 g, 24.05 mmol) in toluene (50 mL) was next added and the mixture stirred at r.t. overnight. Following addition of water, the
10 organic layer was separated, dried (Na_2SO_4), filtered and concentrated to give 8.26 g product as colorless oil (>90% purity by GC-MS analysis). LRMS: m/z calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_4$ 345.19, found 345.3 (M^+). The oil from the last step was dissolved in MeOH (200 mL). Pd/C (1g, 5%) was added. The content was stirred under 1 atm H_2 for 2.5 hrs and then filtered through celite. The solvent
15 was removed under reduced pressure. The residue was purified by flash column chromatography with hexane/ethyl acetate (2/1) to give 6.5 g product as colorless oil (78% yield over two steps). ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 7.47-7.18 (5H, m), 3.70-3.64 (2H, m), 3.54 (3H, s), 3.12 (2H, m), 2.16-2.12 (2H, m), 1.98-1.87 (4H, m), 1.71-1.64 (2H, m), 1.43 (9H, s). LRMS: m/z
20 calcd. for $\text{C}_{20}\text{H}_{29}\text{NO}_4$ 347.2, found 347.3 (M^+).

Synthesis of 5 of the above scheme:

DIBAL-H (38 mL, 1M in toluene, 38 mmol) was cooled to -78°C and added into a solution of 4 (6.5 g, 18.73 mmol) in toluene (80 mL) (also cooled to -78°C with a dry ice-acetone bath to prevent overreduction) dropwise (to
25 keep the internal temperature as low as possible). The content was stirred at -78°C for 2.5 hrs and the reaction was quenched with a cooled MeOH (-78°C) dropwise (the addition needs to be slow to keep the internal temperature low and prevent overreduction). After the addition completed, the content was warmed to r.t. and filtered through celite. The filtrate was washed with brine.
30 The aqueous layer was extracted with ethyl acetate. The combined organic layer was dried with Na_2SO_4 , filtered and concentrated to give 5.72 g product

as light green oil (92% purity by GC-MS analysis). ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 9.53 (1H, s), 7.46-7.25 (5H, m), 3.73-3.67 (2H, m), 3.10-3.05 (2H, m), 2.17-2.09 (4H, m), 1.90-1.86 (2H, t, $J=8.0$ Hz), 1.71-1.64 (2H, m), 1.43 (9H, s). LRMS: m/z calcd. for $\text{C}_{19}\text{H}_{27}\text{NO}_3$ 317.2, found 317.3 (M^+).



5

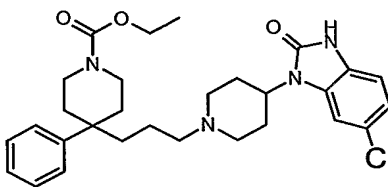
FlexChem Robins Block (24 glass tubes setting) was used for this parallel synthesis. To each glass tube, N_2 was flushed to remove air. Then amines (0.92 eq.), $\text{NaBH}(\text{OAc})_3$ (2 eq.), DCE (1 mL), and aldehyde (1 eq) in THF (1 mL) were added sequentially. The block was sealed and rotated at r.t. overnight. The content was drained through a 24 wells filter plate overnight and the filtrate was collect in the same 24 tubes setting. TFA (1 mL) was added to each tube. The block was sealed and shaken for 80 min. The reaction was complete as evident by LC-MS. The gasket was removed and the solvent and TFA were removed under reduced pressure. Saturated sodium bicarbonate was added to each tube followed by DCM. The organic layer was pipeted out to another 24 tubes block. Acid chlorides or chloroformates (2.7 eq) and PS-DIEA (2.7 eq) were added. The block was sealed and rotated overnight. It was cooled in a freezer for 20 mins before the gasket was removed. PS-Trisamine (2.7 eq) was added and the block was sealed and rotated at r.t. for 4 hrs. The content was filtered, concentrated and the residue was purified with Preparative HPLC. All the compounds were obtained as formic acid salt.

10

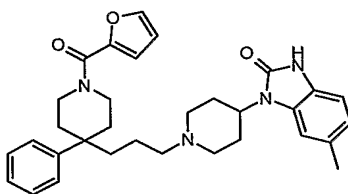
15

20

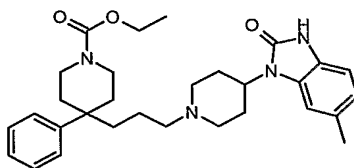
515



Example 744: 2.7 mg product. ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 11.00 (1H, s), 7.82 (1H, s), 7.41-7.34 (5H, m), 7.24-7.20 (2H, m), 6.98-6.93 (3H, m), 6.61-6.59 (1H, m), 4.10-4.02 (1H, m), 3.93-3.88 (2H, m), 2.79 (2H, broad d, $J=15.4$ Hz), 2.26-2.16 (9H, m), 1.92 (2H, broad t, $J=11.5$ Hz), 1.76 (2H, broad t, $J=10.1$ Hz), 10.64-10.55 (4H, m), 1.08-1.02 (2H, broad). HRMS: $\text{C}_{29}\text{H}_{37}\text{ClN}_4\text{O}_3$ calcd. for $(\text{M}+\text{H})^+$ 547.2476, found 547.2480.



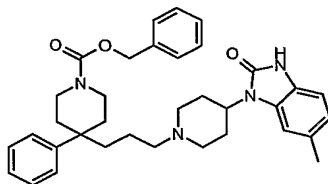
Example 745: 6.7 mg product. ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 10.67 (1H, s), 7.79 (1H, s), 7.39-7.33 (5H, m), 7.21-7.18 (1H, t, $J=6.7$ Hz), 6.97-6.92 (2H, m), 6.78 (2H, dd, $J=29.1$ Hz, 7.9 Hz), 6.59-6.58 (1H, m), 4.06-4.00 (1H, m), 3.90-3.87 (2H, m), 2.79 (2H, broad d, $J=10.5$ Hz), 2.28 (3H, s), 2.25-2.15 (6H, m), 1.90 (2H, broad t, $J=11$ Hz), 1.68-1.63 (2H, m), 1.57-1.48 (4H, m), 1.02 (2H, broad s). HRMS: $\text{C}_{32}\text{H}_{38}\text{N}_4\text{O}_3$ calcd. for $(\text{M}+\text{H})^+$ 527.3022, found 527.3013.



Example 746: 9.6 mg product. ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 10.67 (1H, s), 7.34-7.32 (5H, m), 7.19-7.17 (1H, m), 6.96 (1H, s), 6.77 (2H, dd, $J=28.8$ Hz, 7.7 Hz), 4.02-3.96 (3H, m), 3.06 (2H, m), 2.77 (2H, broad d, $J=10.7$ Hz), 2.28 (3H, s), 2.24-2.04 (6H, m), 1.88 (2H, broad d, $J=11.2$ Hz),

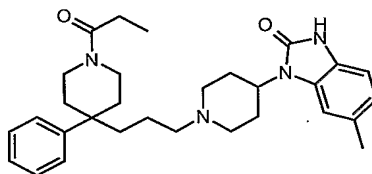
1.68-1.63 (2H, m), 1.57-1.51 (4H, m), 1.14 (3H, t, J=7.1 Hz), 1.04 (2H, m).

HRMS: C₃₀H₄₀N₄O₃ calcd. for (M+H)⁺ 505.3179, found 505.3152.



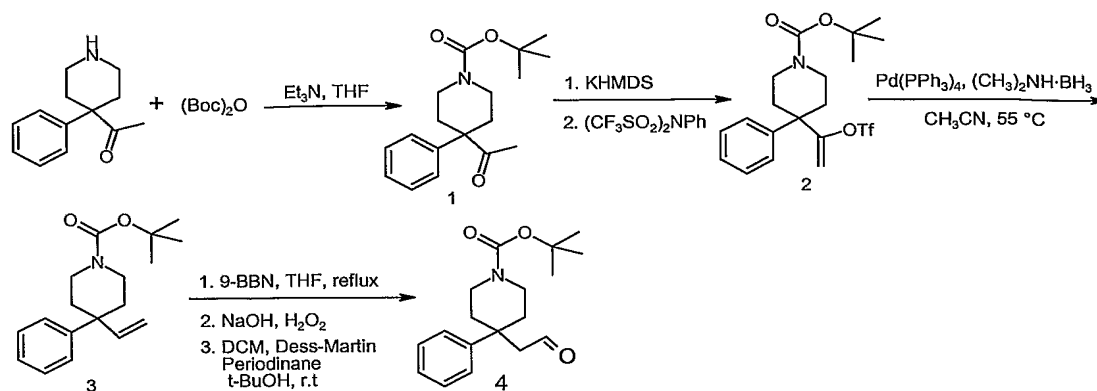
5 Example 747: 5.3 mg product. ¹H NMR (400 MHz, CDCl₃) δ[ppm]:

10.68 (1H, s), 7.39-7.30 (10H, m), 7.23-7.19 (1H, m), 6.98 (1H, s), 6.79 (2H, dd, J=22.4 Hz, 8.9 Hz), 5.06 (2H, s), 4.09-4.01 (1H, m), 3.61 (2H, m), 3.12 (2H, broad s), 2.79 (2H, broad d, J=11.8 Hz), 2.31 (3H, s), 2.28-2.09 (6H, m), 1.91 (2H, t, J=11.3 Hz), 1.70 (2H, t, J=9.9 Hz), 1.60-1.50 (4H, m), 1.07-1.02 (2H, m). HRMS: C₃₅H₄₂N₄O₃ calcd. for (M+H)⁺ 567.3335, found 567.3334.



15 Example 748: 6.9 mg product. ¹H NMR (400 MHz, CDCl₃) δ[ppm]:

10.67 (1H, s), 7.36-7.31 (5H, m), 6.97 (1H, s), 6.78 (2H, dd, J=28.2 Hz, 7.7 Hz), 4.03-4.00 (1H, broad s), 3.78-3.74 (1H, broad), 3.57-3.53 (1H, broad), 3.15-3.10 (1H, m), 3.04-2.99 (1H, m), 2.76 (1H, m), 2.29 (3H, s), 2.27-2.04 (9H, m), 1.85 (1H, broad s), 1.72-1.54 (6H, m), 1.08 (2H, broad s), 0.94 (3H, t, J=7.5 Hz). HRMS: C₃₀H₄₀N₄O₃ calcd. for (M+H)⁺ 489.3229, found 489.3212.

Synthesis of C2-scaffold, BBN methodSynthesis of 1 of the BBN method:

^1H NMR (400 MHz, CDCl_3) δ [ppm]: 7.37-7.34 (2H, m), 7.28-7.25 (3H, m), 3.77-3.73 (2H, m), 3.19-3.13 (2H, m), 2.37-2.33 (2H, m), 1.99-1.93 (2H, m), 1.90 (3H, s), 1.43 (9H, s).

Synthesis of 2 of the BBN method:

To a solution of **1** (2.926 g, 9.66 mmol) in toluene (40 mL) at -78°C , KHMDS (0.5 M in toluene, 21.2 mL) was added dropwise. The content was stirred at -78°C for 10 mins and the dry ice-acetone bath was removed. The stirring was continued for another 15 mins and the content was cooled back to -78°C . $(\text{CF}_3\text{SO}_2)_2\text{NPh}$ (4.14 g, 11.6 mmol) in toluene (30 mL) was added. The resulting light brown content was stirred overnight during which it was warmed to r.t. After work-up with water and ethyl acetate, the residue was purified by flash column chromatography with hexane/EtOAc (20/1 to 10/1) to give 3.20 g product (yield 76%). ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 7.46-7.44 (2H, m), 7.40-7.36 (2H, m), 7.30-7.26 (1H, m), 5.41 (1H, d, $J=5.0$ Hz), 5.32 (1H, d, $J=4.8$ Hz), 3.62-3.56 (2H, m), 3.34 (2H, broad s), 2.30-2.24 (2H, m), 2.14-2.08 (2H, m), 1.43 (9H, s). ^{13}C NMR (400 MHz, d_6 -acetone) δ [ppm]: 205.32, 160.71, 154.36, 140.30, 128.95, 127.60, 127.41, 103.26, 46.17, 40.65, 39.69, 33.04, 27.94.

Synthesis of 3 of the BBN method:

A suspension of K_2CO_3 (0.105 g, 0.76 mmol) and $(\text{CH}_3)_2\text{NH}\cdot\text{BH}_3$ (0.04 g, 0.76 mmol) in CH_3CN (1 mL) in a pressure tube was stirred at r.t. for 10

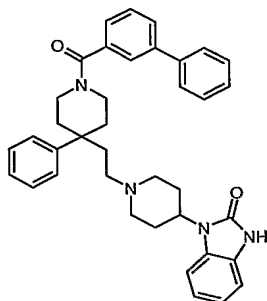
min. A solution of **2** (0.33 g, 0.76 mmol) in CH₃CN (4 mL) was added under nitrogen atmosphere, followed with Pd(PPh₃)₄. The tube was sealed. The content was stirred at 65 °C overnight. After cooling to r.t., the content was filtered and concentrated. The residue was purified by flash column chromatography with hexane/EtOAc (20/1) to give 0.14 g product (64% yield).
5 ¹H NMR (400 MHz, d₆-acetone) δ[ppm]: 7.36-7.29 (4H, m), 7.20-7.16 (1H, m), 5.85 (1H, dd, J=10.8 Hz, 17.7 Hz), 5.11 (1H, d, J=10.9 Hz), 4.95 (1H, d, J=17.6 Hz), 3.50-3.44 (2H, m), 3.41-3.33 (2H, m), 2.07-2.01 (2H, m), 1.96-1.91 (2H, m), 1.43 (9H, s). ¹³CNMR (400 MHz, d₆-acetone) δ[ppm]: 205.39,
10 154.55, 145.93, 145.84, 128.67, 126.88, 114.46, 113.49, 78.67, 43.48, 40.70, 34.98, 28.05. Elemental Analysis: calcd. for C₁₈H₁₅NO₂ C: 75.22%, H: 8.77%, N: 4.87%, found C 75.16%, H 8.81%, N 4.87%. IR is also available.

Synthesis of 4 of the BBN method:

To a solution of **3** (0.267 g, 0.93 mmol) in THF (20 mL) at r.t., 9-BBN
15 (2.8 mL, 0.5 M in THF) was added. The content was heated to reflux overnight. The content was cooled to rt. Sodium hydroxide (0.5 mL, 6.0 M in H₂O) was added, followed with hydrogen peroxide (30% in H₂O, 1 mL). The mixture was stirred at r.t. for 4 hrs, diluted with EtOAc, washed with brine. The organic layer was separated, dried over Na₂SO₄, filtered and
20 concentrated. The residue was purified with chromatotron (1/1 hexane/EtOAc) to give 0.28 g (99% yield) alcohol. ¹H NMR (400 MHz, d₆-acetone) δ[ppm]: 7.29-7.21 (4H, m), 7.16-7.13 (1H, m), 3.61-3.55 (2H, m), 3.26 (2H, t, J=7.3 Hz), 3.08-3.02 (2H, m), 2.10-2.07 (3H, m), 1.78 (2H, t, J=7.4 Hz), 1.71-1.64 (2H, m), 1.37 (9H, s).

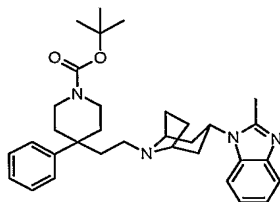
To a suspension of Dess-Martin periodinane in dichloromethane (15
25 mL) at r.t., t-BuOH was added and the content was stirred for 10 mins. A solution of the alcohol in dichloromethane was added dropwise at r.t. and stirred for 15 mins. The content was diluted with Et₂O, washed with 1.3 N NaOH, dried over Na₂SO₄, filtered, and concentrated. The residue was
30 purified by flash column chromatography with hexane/EtOAc (3/1) to give 0.2 g product as oil (72% yield).

519



Example 749: HRMS calc. for $C_{38}H_{41}N_4O_2$ (M+H)⁺ 585.3230, found 585.3201.

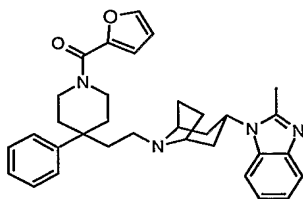
5



Example 750: HRMS calc. for $C_{32}H_{37}N_4O_2$ (M+H)⁺ 509.2917, found 509.2948. ¹H NMR (400 MHz, CDCl₃) δ[ppm]: 7.92 (1H, s), 7.85 (1H, broad s), 7.71-7.23 (6 H, m), 4.57-4.42 (1H, m), 3.71-3.63 (4H, m), 3.23-3.17 (2H, m), 2.85-2.76 (2H, m), 2.59 (3H, s), 2.46-2.45 (2H, m), 2.07-1.98 (4H, m), 1.90-1.87 (2H, m), 1.80-1.70 (6H, m), 1.42 (9H, s). MS calcd for $C_{33}H_{45}N_4O_2$ (M+H)⁺ 529, found 529.

10

Example 707

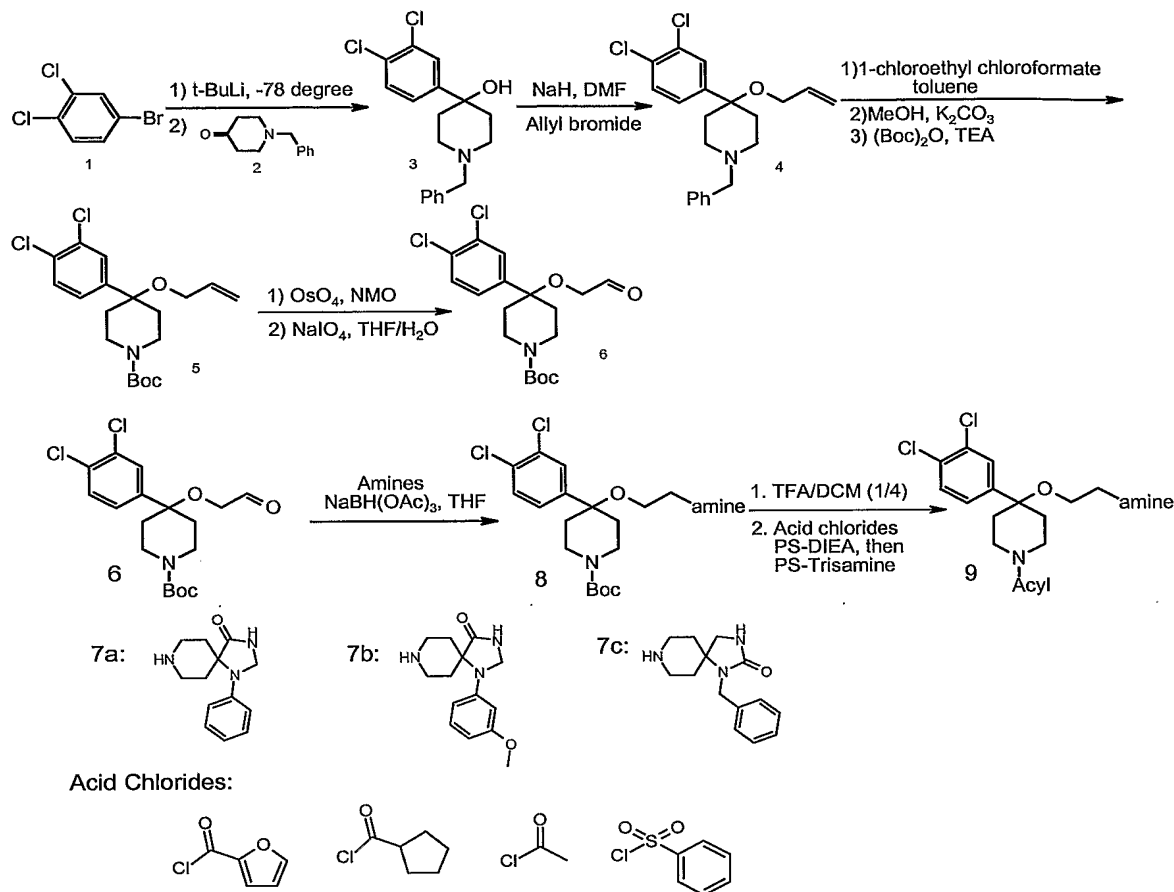


15

¹H NMR (400 MHz, CDCl₃) δ[ppm]: 7.90 (1H, s), 7.51 (1H, s), 7.46-7.35 (7H, m), 6.99-6.94 (1H, m), 6.46 (1H, s), 4.49-4.43 (1H, m), 4.14-4.11 (2H, m), 3.48 (2H, s), 3.28 (2H, s), 2.56 (3H, s), 2.40-2.34 (4H, m), 2.19 (2H,

broad s), 1.93-1.85 (5H, m), 1.63-1.57 (5H, m). MS calcd. for $C_{33}H_{39}N_4O_2$ (M+H)⁺ 523, found 523.

O-linked piperidines were synthesized according to the scheme depicted below.



Synthesis of 3 in the scheme for O-linked piperidines:

t-BuLi (31.2 mL, 1.7 M in pentane, 53.1 mmol) was added to Et₂O at –
78°C, followed by 1-bromo-3,4-dichlorobenzene (3.4 mL, 26.6 mmol)
dropwise. The content was stirred at –78°C for another 5 mins before 2 (4.92
mL, 26.6 mmol) was added. It was stirred and gradually warmed up to r.t.
overnight. Water was added. The mixture was extracted with ethyl acetate.
The combined organic layer was dried over sodium sulfate, filtered and
concentrated to afford 9 g product as light brown oil (100% yield). ¹H NMR

(400 MHz, CDCl_3) δ [ppm]: 7.62 (1H, d, $J=2.2$ Hz), 7.39 (1H, d, $J=8.4$ Hz), 7.36-7.30 (5H, m), 7.28-7.24 (1H, m), 3.58 (2H, s), 2.79 (2H, d, $J=11.4$ Hz), 2.44 (2H, t, $J=6.8$ Hz), 2.11 (2H, td, $J=13.4$ Hz, 3.5 Hz), 1.76 (1H, s), 1.68 (2H, dd, $J=13.9$ Hz, 2.2 Hz).

5 Synthesis of 4 in the scheme for O-linked piperidines:

To a solution of 3 (9.0 g, 26.87 mmol) in DMF, NaH (2.15 g, 60% in mineral oil, 53.73 mmol) and allyl bromide (2.8 mL, 32.24 mmol) were added. The content was stirred at r.t. overnight. The reaction was quenched with water, extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography with hexane/ethyl acetate (3/1) to give 7.47 g (74%) product as yellow oil. ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 7.49 (1H, d, $J=2.0$ Hz), 7.40 (1H, d, $J=8.4$ Hz), 7.35-7.27 (5H, m), 7.27-7.23 (1H, m), 5.91-5.82 (1H, m), 5.28 (1H, dd, $J=17.2$ Hz, 1.6 Hz), 3.58-3.55 (4H, m), 2.74 (2H, d, $J=11.0$ Hz), 2.50-2.43 (2H, m), 1.98 (4H, d, $J=3.3$). LRMS: calcd. for $\text{C}_{21}\text{H}_{24}\text{Cl}_2\text{NO}$ ($\text{M}+\text{H}$) $^+$ 376, found 376.

15 Synthesis of 5 in the scheme for O-linked piperidines:

A solution of 4 (7.47 g, 199.92 mmol) in dichloroethane (120 mL) was cooled to 0 °C, 1-chloroethyl chloroformate (4.22 mL, 39.16 mmol) was added dropwise. The content was stirred at 0 °C for 15 mins and then heated to reflux for 1 hr. The solvent was removed under reduced pressure. The residue was redissolved in MeOH and the content was refluxed for 1 hr. After cooling to r.t., water and ethyl acetate were added (saw precipitate). The content was filtered to give crystalline pale-white solid. To a suspension of the solid in THF (150 mL), triethyl amine (8.35 mL, 60 mmol) and $(\text{Boc})_2\text{O}$ were added. The content was stirred at r.t overnight. Water (100 mL) and brine (100 mL) were added. The mixture was extracted with ethyl acetate. The combined organic layer was washed with 0.1 N NaOH (2x), dried over sodium sulfate, filtered and concentrated. Flash column chromatography with hexane/ethyl acetate (9/1) gave 3.19 g product as colorless oil (42% yield).

20 ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 7.45 (1H, d, $J=2.0$ Hz), 7.42 (1H, d, $J=8.4$ Hz), 7.22 (1H, dd, $J=8.4$ Hz, 2.2 Hz), 5.90-5.80 (1H, m), 5.27 (1H, dd, $J=17.2$

25

30

Hz, 1.6 Hz), 5.14 (1H, dd, J=10.5 Hz, 1.3 Hz), 3.99 (2H, d, J=13.0 Hz), 3.58 (2H, d, J=5.1 Hz), 3.18 (2H, d, J=9.2 Hz), 1.98 (2H, d, J=12.7 Hz), 1.80 (2H, td, J=13.2 Hz, 5.6 Hz), 1.46 (9H, s). LRMS: calcd. for $C_{19}H_{26}Cl_2NO_3$ (M+H)⁺ 386, found 386.

5 Synthesis of 6 in the scheme for O-linked piperidines:

To a solution of 5 (3.19 g, 8.29 mmol) in acetone (80 mL), *t*-BuOH (20 mL) and water (20 mL) were added, followed by OsO₄ (2.5% in *t*-BuOH, 5.2 mL, 0.42 mmol). The content was stirred at r.t for 5 mins and then NMO (1.94 g, 16.6 mmol) was added. It was stirred for another 2 hrs at r.t. The reaction
10 was quenched with saturated NaHSO₃ (100 mL), extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated to give 3.5 g colorless oil. To a solution of the oil in THF (100 mL), water (25 mL) was added, followed by NaIO₄ (4.44 g, 20.73 mmol). The content was stirred at r.t for 4 hrs. Water (100 mL) was added. The mixture was extracted with ethyl acetate. The
15 organic layer was washed with 1:1 water:brine, dried over sodium sulfate, filtered and concentrated to give 2.66 g product (83% yield). ¹H NMR (400 MHz, CDCl₃) δ[ppm]: 9.66 (1H, s), 7.46-7.43 (2H, m), 7.24-7.22 (2H, m), 4.00 (2H, broad d, J=10.6 Hz), 3.69 (2H, s), 3.22 (2H, broad d, J=11.7 Hz), 2.03-2.00 (2H, m), 1.90-1.83 (2H, m), 1.46 (9H, s).

20 Synthesis of 8a in the scheme for O-linked piperidines:

To a solution of 6 (0.885g, 2.29 mmol) in THF (10 mL), amine 7a (0.792 g, 3.44 mmol) was added. The content was stirred at r.t. for 5 mins and then NaBH(OAc)₃ (1.214 g, 5.73 mmol) was added. The content was stirred at r.t. overnight. The reaction was quenched with saturated sodium
25 bicarbonate solution, extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated. Chromatograph purification with 5%MeOH+0.5%ammonium hydroxide in methylene chloride gave 0.62 g product as white solid. ¹H NMR (400 MHz, CDCl₃) δ[ppm]: 7.89 (1H, s), 7.45-7.39 (2H, m), 7.26 (3H, broad s), 6.90-6.84 (3H, m), 4.72 (2H, s), 4.09-3.95 (2H, broad), 3.19 (4H, broad s), 2.87-2.63 (8H, m), 2.00-1.96 (2H, m), 1.77-1.67 (4H, m), 1.45 (9H, s). LRMS: calcd. for $C_{31}H_{41}Cl_2N_4O_4$ 603, found 603.
30

Synthesis of 8b in the scheme for O-linked piperidines:

0.48 g product as white solid. ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 7.45-7.41 (2H, m), 7.29 (1H, d, $J=7.5$ Hz), 7.19-7.17 (1H, broad), 6.59-6.57 (1H, broad), 6.43-6.38 (2H, m), 6.25 (1H, s), 4.70 (2H, s), 4.02-3.93 (2H, broad), 3.78 (3H, s), 3.18 (4H, broad s), 2.85-2.62 (8H, m), 2.04-1.97 (2H, broad), 1.78-1.66 (4H, m), 1.46 (9H, s). LRMS: calcd. for $\text{C}_{32}\text{H}_{43}\text{Cl}_2\text{N}_4\text{O}_5$ 633, found 633.

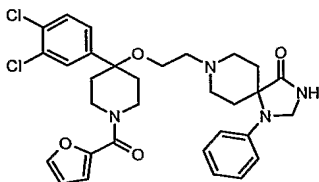
Synthesis of 8c in the scheme for O-linked piperidines:

0.56 g product as white solid. ^1H NMR (400 MHz, CDCl_3) δ [ppm]: 7.44 (1H, d, $J=1.6$ Hz), 7.36 (1H, d, $J=8.5$ Hz), 7.32-7.28 (4H, m), 7.22-7.17 (2H, m), 4.37 (2H, s), 3.96 (2H, broad s), 3.28 (2H, s), 3.10 (4H, broad), 2.76 (2H, d, $J=11.2$ Hz), 2.47 (2H, t, $J=5.7$ Hz), 2.04-1.91 (4H, m), 1.88-1.74 (4H, m), 1.45 (9H, s). LRMS: calcd. for $\text{C}_{32}\text{H}_{43}\text{Cl}_2\text{N}_4\text{O}_4$ 617, found 617.

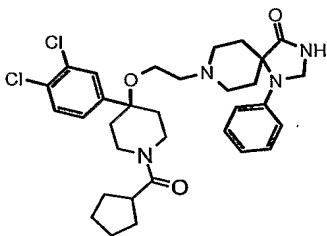
Parallel Synthesis using Robins Block

8a-8c were deprotected with TFA (1 mL) in dichloromethane (4 mL) at r.t for 20 min. Saturated sodium bicarbonate solution was added. The mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was dissolved in dichloromethane (4 mL) and added to Robins block (1 mL/each tube). To each tube were added PS-DIEA (3 eq) and acid chloride (1.5 eq.). The block was sealed and rotated overnight. It was cooled in a freezer for 15 mins and opened. PS-Trisamine (3 eq.) was added. The block was sealed and rotated for 4 hrs. The content in each tube was poured into a 24-wells filtering block and drained overnight. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC to give the desired product.

524

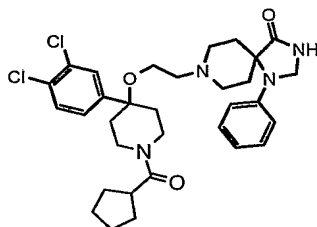
Example 752

¹H NMR (400 MHz, CD₃OD) δ[ppm]: 8.47 (1H, s), 7.67 (2H, d, J=2.2 Hz), 7.45 (1H, dd, J=8.4 Hz, 2.0 Hz), 7.26 (2H, t, J=8.2 Hz), 7.02-6.99 (3H, m), 6.89 (1H, t, J=7.4 Hz), 6.57 (1H, dd, J=3.5 Hz, 1.8 Hz), 4.72 (2H, s), 4.39 (2H, broad s), 3.75 (2H, td, J=12.6 Hz, 2.8 Hz), 3.44-3.29 (6H, m), 3.22 (2H, t, J=5.0 Hz), 2.79 (2H, td, J=14.5 Hz, 4.8 Hz), 2.24 (2H, d, J=13.5 Hz), 2.01-1.94 (4H, m). HRMS calcd. for C₃₁H₃₅Cl₂N₄O₄ (M+H)⁺ 597.2035, found 597.2045.

Example 753

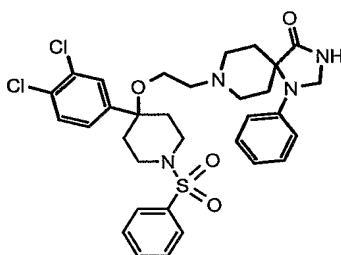
¹H NMR (400 MHz, CD₃OD) δ[ppm]: 8.55 (1H, s), 7.69 (1H, d, J=1.8 Hz), 7.58 (1H, dd, J=5.7 Hz, 1.8 Hz), 7.47 (1H, d, J=8.4 Hz), 7.30 (2H, t, J=8.0 Hz), 7.04 (2H, d, J=8.2 Hz), 6.92 (1H, t, J=8.2 Hz), 4.74 (2H, s), 4.45 (1H, broad d, J=12.2), 3.98 (1H, t, J=13.5 Hz), 3.72 (2H, t, J=12.1 Hz), 3.58 (1H, t, J=8.2 Hz), 3.43-3.32 (6H, m), 3.21 (2H, broad s), 3.16-3.08 (1H, m), 2.81 (2H, broad t, J=10.6 Hz), 2.32-2.15 (3H, m), 2.03-1.30 (10H, m). HRMS calcd. for C₃₂H₄₁Cl₂N₄O₃ (M+H)⁺ 599.2555, found 599.2520.

525

Example 754

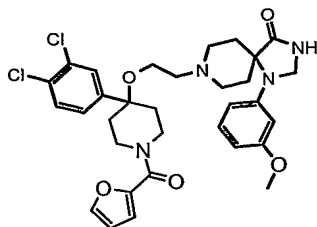
HRMS calcd. for $C_{28}H_{35}Cl_2N_4O_3$ ($M+H$)⁺ 545.2084, found 545.2062.

Elemental Analysis: calcd. for $C_{29}H_{37}Cl_2N_4O_5$ (formic acid salt) C 58.88%, H 6.13%, N 9.47%; found C 58.19%, H 6.13%, N 9.27%.

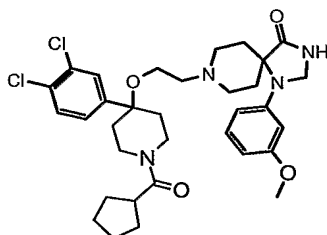
Example 755

¹HNMR (400 MHz, CD₃OD) δ[ppm]: 8.48 (1H, broad s), 7.86-7.79 (2H, m), 7.62-7.51 (5H, m), 7.41-7.32 (3H, m), 7.06-6.95 (3H, m), 4.76 (2H, s), 3.76 (2H, d, J=19.6 Hz), 3.51-2.99 (8H, m), 2.71 (2H, t, J=11.2 Hz), 2.58 (2H, td, J=14.5 Hz, 0.6 Hz), 2.20 (2H, t, J=13.5 Hz), 2.02 (2H, td, J=12.6 Hz, 4.1 Hz), 1.75 (2H, d, J=14.6 Hz). HRMS calcd for $C_{32}H_{37}Cl_2N_4O_4S$ ($M+H$)⁺ 643.1912, found 643.1926. Elemental Analysis for $C_{33}H_{38}Cl_2N_4O_4S$ (formic acid salt) calcd. C 57.47%, H 5.55%, N 8.12%; found C 56.94%, H 5.68%, N 8.04%.

526

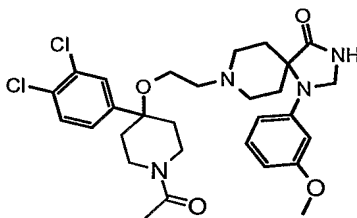
Example 756

¹HNMR (400 MHz, CD₃OD) δ[ppm]: 8.51 (1H, broad s), 7.70 (1H, s), 7.59 (1H, d, J=8.5 Hz), 7.84 (1H, dd, J=6.5 Hz, 1.8 Hz), 7.21 (1H, t, J=8.1 Hz), 1.05 (1H, d, J=3.5 Hz), 6.68 (2H, dd, 8.3 Hz, 1.4 Hz), 6.61 (1H, dd, J=3.3 Hz, 1.7 Hz), 6.54-6.49 (3H, m), 4.72 (2H, s), 4.43 (2H, broad d, J=11.8 Hz), 3.85-3.75 (5H, m), 3.46-3.27 (8H, m), 2.85 (2H, td, J=14.5 Hz, 3.5 Hz), 2.28 (2H, d, J=13.5 Hz), 2.06-1.95 (4H, m). HRMS calcd. for C₃₂H₃₇Cl₂N₄O₅ (M+H)⁺, 627.2141 found 627.2128. Elemental Analysis for C₃₃H₃₈Cl₂N₄O₇ (formic acid salt) calcd. C 58.84%, H 5.69%, N 8.32%; found C 58.21% H 5.76%, N 8.26%.

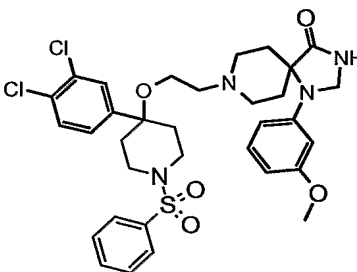
Example 757

¹HNMR (400 MHz, CD₃OD) δ[ppm]: 8.51 (1H, broad s), 7.69 (1H, d, J=1.8 Hz), 7.58 (1H, d, J=8.4 Hz), 7.47 (1H, dd, J=8.4 Hz, 1.8 Hz), 7.22 (1H, t, J=8.1 Hz), 6.67 (1H, broad d, J=8.1 Hz), 6.55-6.50 (4H, m), 4.73 (2H, s), 4.45 (1H, d, J=12.8 Hz), 4.00 (1H, d, J=14.4 Hz), 3.79-3.62 (5H, m), 3.55 (1H, t, J=7.1 Hz), 3.45-3.32 (6H, m), 3.22-3.11 (4H, m), 2.80 (2H, td, J=14.3 Hz, 3.5 Hz), 2.22 (2H, broad d, J=11.6 Hz), 1.99-1.62 (10H, m). HRMS calcd. for C₃₃H₄₃Cl₂N₄O₄ (M+H)⁺ 629.2661, found 629.2664.

527

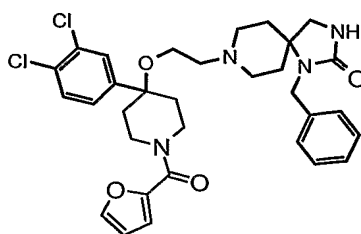
Example 758

¹HNMR (400 MHz, CD₃OD) δ[ppm]: 8.50 (1H, broad s), 7.69 (1H, d, J=1.8 Hz), 7.58 (1H, d, J=8.5 Hz), 7.47 (1H, dd, J=8.4 Hz, 1.8 Hz), 7.22 (1H, t, J=8.1 Hz), 6.68 (1H, dd, J=8.3 Hz, 1.6 Hz), 6.55-6.50 (4H, m), 4.73 (2H, s), 4.43 (1H, d, J=13.1 Hz), 3.86-3.74 (6H, m), 3.59 (1H, t, J=10.9 Hz), 3.44-3.32 (4H, m), 3.23 (2H, s), 3.12 (1H, t, J=9.4 Hz), 2.85-2.77 (2H, m), 2.25-2.25-2.17 (5H, m), 2.04-1.75 (4H, m). HRMS calcd. for C₂₉H₃₇Cl₂N₄O₄ (M+H)⁺ 575.2192, found 575.2190. Elemental Analysis calcd. for C₃₀H₃₉Cl₂N₄O₆ (formic acid salt) C 57.97%, H 6.16%, N 9.01%; found C 57.83%, H 6.31%, N 8.94%.

Example 759

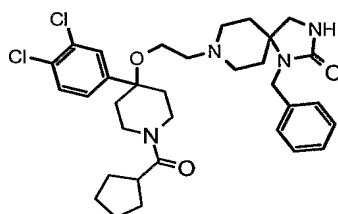
¹HNMR (400 MHz, CD₃OD) δ[ppm]: 8.47 (1H, broad s), 7.82-7.78 (2H, m), 7.61 (1H, d, J=1.8 Hz), 7.57-7.52 (4H, m), 7.40 (1H, dd, J=8.4 Hz, 1.8 Hz), 7.26 (1H, t, J=8.3 Hz), 6.64 (1H, dd, J=8.3 Hz, 1.8 Hz), 6.58 (1H, broad d, J=8.2 Hz), 6.50 (1H, s), 4.74 (2H, s), 3.82 (3H, s), 3.72 (2H, d, J=11.8 Hz), 3.41-3.35 (2H, m), 3.25 (2H, t, J=4.7 Hz), 3.04 (2H, broad d, J=11.0 Hz), 2.91 (2H, broad s), 2.71 (2H, t, J=10.7 Hz), 2.54 (2H, td, J=14.3 Hz, 4.8 Hz), 2.22 (2H, d, J=13.4 Hz), 2.00 (2H, td, J=12.7 Hz, 3.1 Hz), 1.73 (2H, d, J=14.3 Hz). HRMS: calcd. for C₃₃H₃₉Cl₂N₄O₄S (M+H)⁺ 673.2018, found 673.2002.

Example 760



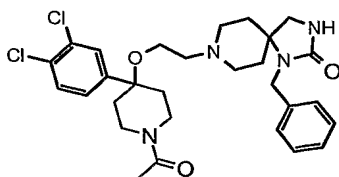
¹H NMR (400 MHz, CD₃OD) δ [ppm]: 8.43 (1H, broad s), 7.70 (1H, s), 7.65 (1H, d, J=1.6 Hz), 7.55 (1H, d, J=14.7 Hz), 7.41 (1H, dd, J=8.4 Hz, 1.8 Hz), 7.36-7.29 (4H, m), 7.26-7.22 (1H, m), 7.05 (1H, d, J=3.3 Hz), 6.62-6.59 (1H, m), 4.45-4.41 (4H, m), 3.40 (2H, s), 3.33-3.27 (4H, m), 3.05 (2H, d, J=12.1 Hz), 2.80 (2H, t, J=4.8 Hz), 2.40 (2H, t, J=12.5 Hz), 2.22 (2H, d, J=13.5 Hz), 2.05-1.94 (4H, m), 1.60 (2H, d, J=13.1 Hz). HRMS: calcd. for C₃₂H₃₇Cl₂N₄O₄ (M+H)⁺ 611.2192, found 611.2205. Elemental Analysis: calcd. for C₃₃H₃₉Cl₂N₄O₆ (formic acid salt) C 60.27%, H 5.82%, N 8.52%; found C 61.08%, H 5.91%, N 8.44%.

Example 761



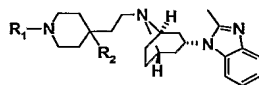
15 ¹HNMR (400 MHz, CD₃OD) δ[ppm]: 7.59 (1H, d, J=2.0 Hz), 7.46 (1H,
d, J=8.4 Hz), 7.37-7.27 (5H, m), 7.23-7.20 (1H, m), 4.44-4.37 (3H, m), 3.97
(1H, d, J=12.8 Hz), 3.54-3.45 (2H, m), 3.34 (2H, s), 3.23-3.18 (2H, m), 3.11-
3.00 (1H, m), 2.86 (2H, broad d, J=11.4 Hz), 2.60 (2H, t, J=15.5 Hz), 2.17-
2.11 (4H, m), 1.95-1.49 (14H, m). HRMS: calcd. for C₃₃H₄₃Cl₂N₄O₃ (M+H)⁺
20 613.2712, found 613.2723.

529

Example 762

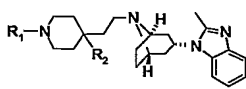
^1H NMR (400 MHz, CD_3OD) δ [ppm]: 8.38 (1H, broad), 7.63 (1H, d, $J=1.7$ Hz), 7.51 (1H, d, $J=8.4$ Hz), 7.41-7.25 (6H, m), 4.52–4.41(3H, m), 3.80 (2H, t, $J=11.8$ Hz), 3.53 (1H, t, $J=13.2$ Hz), 3.38 (2H, d, $J=10.1$ Hz), 3.26 (2H, broad s), 3.09-2.95 (4H, m), 2.83-2.67 (2H, m), 2.45-2.30 (2H, m), 2.17-1.81 (8H, m), 1.58-1.51 (2H, m). HRMS calcd for $\text{C}_{29}\text{H}_{37}\text{Cl}_2\text{N}_4\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 559.2243, found 559.2240.

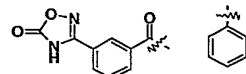
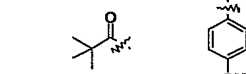
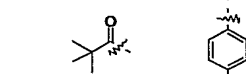
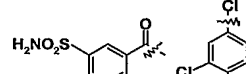
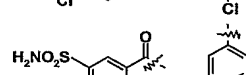
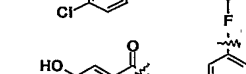
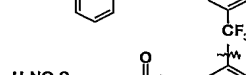
10 Examples 763-774 were synthesized analogously to example 16 and 703.



Example	R ¹	R ²	ESI-MS m/z (M+H)
763			549
764			569
765			563
766			627
767			613

530



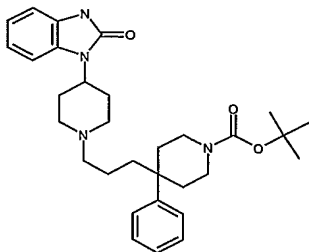
Example #	Chemical Structure	Example #
768		617
769		543
770		548
771		716
772		665
773		645
774		681

The following compounds were synthesized using chemistry described elsewhere in this application.

5

Example 775

tert-butyl 4-{3-[4-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]propyl}-4-phenylpiperidine-1-carboxylate

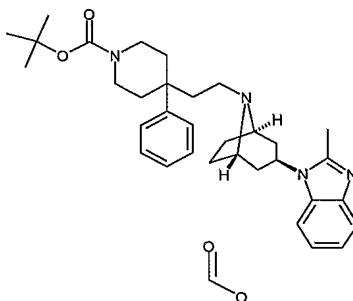


10

^1H NMR (400MHz, CDCl_3) δ 10.43 (m, 1H), 7.32-6.98 (m, 10H), 4.28 (m, 1H), 3.65 (m, 2H), 3.09 (m, 2H), 2.87-2.84 (m, 2H), 2.37 (m, 2H), 2.18 (m, 4H), 1.95 (m, 1H), 1.70 (m, 4H), 1.54 (m, 2H), 1.41 (s, 9H), 1.14-1.00 (m, 2H). MS (electrospray +) 519.27 (M+1).

Example 776

tert-butyl 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxylate



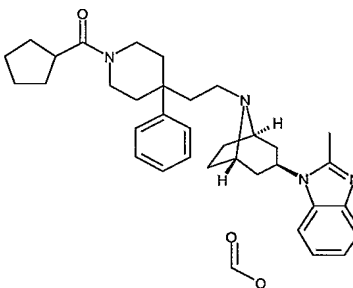
5

^1H NMR (300MHz, methanol- d_4) δ 7.76 (m, 1H), 7.59-7.38 (m, 5H), 7.39-7.13 (m, 3H), 4.80-4.63 (m, 1H), 3.95 (m, 2H), 3.81-3.63 (m, 2H), 3.20-3.09 (m, 2H), 2.80-2.55 (m, 7H), 2.28-2.20 (m, 2H), 2.13-1.92 (m, 8H), 1.90-1.75 (m, 2H), 1.47 (s, 9H). MS (electrospray +) 529.60 (M+1).

10

Example 777

1-((1R,5S)-8-{2-[1-(cyclopentylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



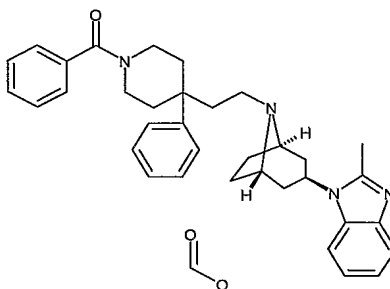
15

^1H NMR (300 MHz, methanol- d_4) δ 7.65 (m, 1H), 7.48-7.32 (m, 5H), 7.26-7.06 (m, 3H), 4.65 (m, 1H), 4.04-3.71 (m, 4H), 3.20 (m, 1H), 3.09-2.94 (m, 2H), 2.71-2.46 (m, 7H), 2.32-2.16 (m, 2H), 2.10-1.86 (m, 8H), 1.83-1.47 (m, 10H). HR MS (M+H) calc: 525.3593, found 525.3595, delta 0.2mmu.

532

Example 778

1-((1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

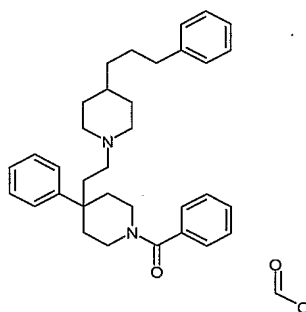


5 ^1H NMR (300 MHz, methanol- d_4) δ 7.80 (m, 1H), 7.62-7.17 (m, 13H), 4.74 (m, 1H), 4.30-4.13 (m, 1H), 4.02 (m, 2H), 3.71-3.55 (m, 1H), 3.32 (s, 2H), 2.84-2.71 (m, 4H), 2.65 (s, 3H), 2.45 (m, 1H), 2.29-1.81 (m, 11H). HRMS (M+H) calc: 533.3280, found 533.3267, delta 1.3 mmu.

10

Example 779

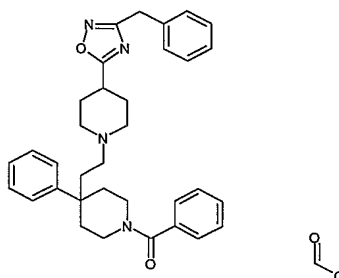
1-benzoyl-4-phenyl-4-{2-[4-(3-phenylpropyl)piperidin-1-yl]ethyl}piperidine



15 ^1H NMR (300 MHz, methanol- d_4) δ 7.45-7.33 (m, 9H), 7.29-7.17 (m, 3H), 7.14-7.05 (m, 3H), 4.15 (m, 1H), 3.55 (m, 1H), 3.30-3.15 (m, 4H), 2.58-2.33 (m, 7H), 2.26-2.18 (m, 1H), 2.00-1.73 (m, 6H), 1.59 (m, 2H), 1.41 (m, 1H), 1.29-1.15 (m, 4H). HRMS (M+H) calc: 495.3375, found 495.3376, delta 0.1 mmu.

Example 780

1-benzoyl-4-{2-[4-(3-benzyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]ethyl}-4-phenylpiperidine

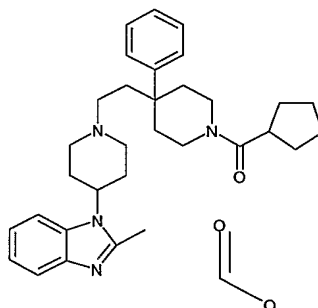


5 ^1H NMR (300 MHz, methanol- d_4) δ 7.45-7.39 (m, 9H), 7.29-7.18 (m, 6H), 4.14 (m, 1H), 4.01 (s, 2H), 3.58 (m, 1H), 3.30-3.16 (m, 3H), 3.02-2.86 (m, 3H), 2.38 (m, 1H), 2.20 (m, 4H), 2.06-1.98 (m, 2H), 1.91-1.74 (m, 6H). HRMS ($\text{M}+\text{H}$) calc: 535.3073, found 535.3098, delta 2.5 mmu.

10

Example 781

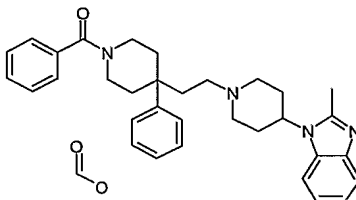
1-(1-{2-[1-(cyclopentylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}piperidin-4-yl)-2-methyl-1H-benzimidazole



15 ^1H NMR (400 MHz, methanol- d_4) δ 7.65 (m, 1H), 7.52-7.44 (m, 2H), 7.39-7.30 (m, 5H), 7.24-7.14 (m, 1H), 4.89 (m, 1H), 4.02-3.91 (m, 1H), 3.81-3.75 (m, 1H), 3.62-3.53 (m, 2H), 3.13-3.02 (m, 3H), 3.00-2.73 (m, 8H), 2.26-2.09 (m, 6H), 1.84-1.49 (m, 10H), 1.24-1.13 (m, 1H). HRMS ($\text{M}+\text{H}$) calc: 499.3435, found 499.3434, delta 0.1mmu.

Example 782

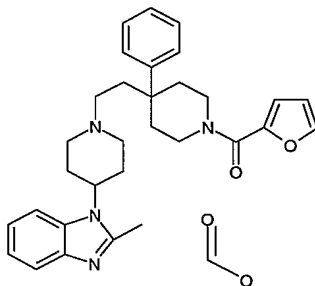
1-{1-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]piperidin-4-yl}-2-methyl-1H-benzimidazole



¹H NMR (400 MHz, methanol-d₄) δ 7.63 (m, 1H), 7.51-7.45 (m, 3H), 7.40-7.32 (m, 6H), 7.24-7.16 (m, 2H), 6.91 (s, 1H), 6.70 (s, 1H), 4.89 (m, 1H), 4.89 (m, 1H), 4.10 (m, 1H), 3.80 (m, 1H), 3.60 (m, 2H), 3.37-3.24 (m, 3H), 3.10 (m, 3H), 2.95-2.86 (m, 2H), 2.77 (m, 2H), 2.31 (m, 2H), 2.22-2.13 (m, 4H), 1.92-1.87 (m, 2H), 1.23-1.18 (m, 1H). HRMS (M+H) calc: 507.3126, found 507.3115, delta 1.1mmu.

Example 783

1-(1-{2-[1-(2-furoyl)-4-phenylpiperidin-4-yl]ethyl}piperidin-4-yl)-2-methyl-1H-benzimidazole

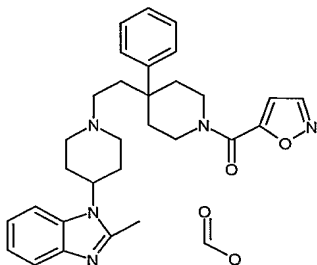


¹H NMR (400 MHz, methanol-d₄) δ 8.22 (m, 1H), 7.67 (m, 1H), 7.58 (s, 1H), 7.60-7.48 (m, 2H), 7.42-7.31 (m, 4H), 7.22 (m, 1H), 6.91 (m, 1H), 6.49 (s, 1H), 4.89 (m, 1H), 4.06 (m, 2H), 3.68-3.56 (m, 2H), 3.08 (m, 2H), 3.00-2.75 (m, 7H), 2.56 (s, 3H), 2.32-2.18 (m, 5H), 1.88 (m, 2H). MS (electrospray +) 523.42 (M+1).

535

Example 784

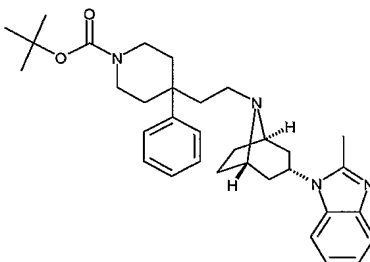
1-(1-{2-[1-(isoxazol-5-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}piperidin-4-yl)-2-methyl-1H-benzimidazole



¹H NMR (400 MHz, methanol-d₄) δ 7.64 (m, 1H), 7.46 (m, 2H), 7.41-7.27 (m, 7H), 7.24-7.10 (m, 1H), 4.88 (m, 1H), 4.07 (m, 2H), 3.61-3.49 (m, 1H), 3.20 (s, 2H), 3.11-3.00 (m, 2H), 2.93-2.84 (m, 2H), 2.79-2.71 (m, 4H), 2.30 (m, 1H), 2.21-2.09 (m, 4H), 1.92-1.75 (m, 2H), 1.21 (m, 1H). HRMS (M+H) calc: 498.2869, found 498.2845, delta 2.4 mmu.

Example 785

tert-butyl 4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxylate

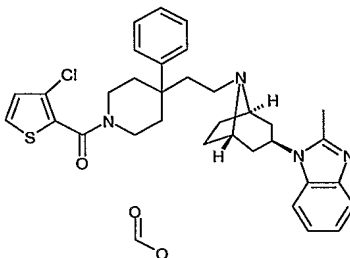


¹H NMR (400 MHz, CDCl₃) δ 7.22 (m, 1H), 6.91-6.68 (m, 8H), 4.15 (m, 1H), 3.23-3.18 (m, 2H), 2.82-2.67 (m, 4H), 2.12 (s, 3H), 1.97-1.87 (m, 2H), 1.76-1.64 (m, 2H), 1.51-1.29 (m, 10H), 1.17-1.13 (m, 2H), 1.00 (s, 9H). MS (electrospray +) 529.61 (M+1).

536

Example 786

1-[(1R,5S)-8-(2-{1-[(3-chlorothiophen-2-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

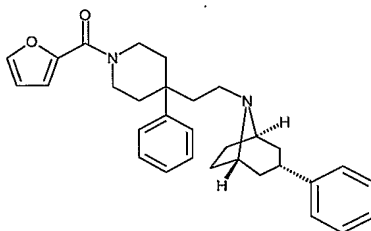


5 ^1H NMR (400 MHz, methanol- d_4) δ 7.66 (m, 1H), 7.56-7.43 (m, 5H), 7.34-7.23 (m, 3H), 7.01 (m, 2H), 4.72 (m, 1H), 4.10 (m, 2H), 3.41-3.28 (m, 4H), 2.90 (m, 2H), 2.79 (m, 2H), 2.68 (s, 3H), 2.41-1.94 (m, 12H). HRMS (M+H) calc: 573.2455, found 573.2452, delta 0.3 mmu.

10

Example 787

(1R,5S)-8-{2-[1-(2-furoyl)-4-phenylpiperidin-4-yl]ethyl}-3-phenyl-8-azabicyclo[3.2.1]octane

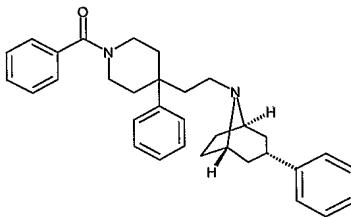


15 ^1H NMR (400 MHz, CDCl_3) δ 7.38 (s, 1H), 7.31-7.00 (m, 10H), 6.86 (m, 1H), 6.38 (m, 1H), 3.98 (m, 1H), 3.48-3.27 (m, 2H), 3.12 (m, 2H), 2.96-2.86 (m, 1H), 2.38-2.15 (m, 4H), 1.98 (m, 3H), 1.86-1.76 (m, 4H), 1.60-1.50 (m, 4H), 1.29 (m, 2H). HRMS (M+H) calc: 469.2855, found 469.2858, delta 0.3 mmu.

537

Example 788

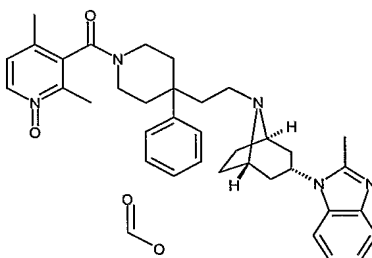
(1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-3-phenyl-8-azabicyclo[3.2.1]octane



¹H NMR (400 MHz, CDCl₃) δ 7.44-7.26 (m, 13H), 7.15 (m, 2H), 4.16-4.12 (m, 1H), 3.58 (m, 1H), 3.45 (m, 1H), 3.32-3.16 (m, 3H), 3.01 (m, 1H), 2.41-2.26 (m, 3H), 2.16-1.86 (m, 5H), 1.78-1.63 (m, 5H), 1.38-1.24 (m, 3H). HRMS (M+H) calc: 479.3062, found 479.3057, delta 0.6 mmu.

Example 789

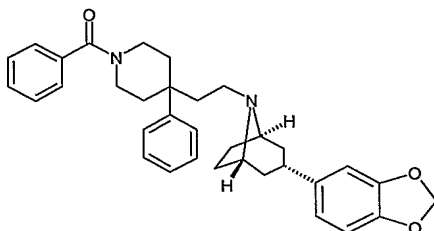
1-[(1R,5S)-8-(2-{1-[(2,4-dimethyl-1-oxidopyridin-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



¹H NMR (500 MHz, DMSO-d₆) δ 8.18 (m, 1H), 7.49 (m, 1H), 7.37 (m, 5H), 7.26-7.08 (m, 4H), 4.51 (m, 1H), 4.02-3.89 (m, 2H), 3.60-3.44 (m, 2H), 3.35-3.21 (m, 4H), 3.02 (m, 1H), 2.54-2.38 (m, 4H), 2.38-2.28 (m, 3H), 2.25-2.09 (m, 3H), 2.03 (m, 2H), 1.87-1.70 (m, 8H), 1.58 (m, 2H). HRMS (M+H) calc: 578.3495, found 578.3519, delta 2.4 mmu.

Example 790

(1R,5S)-3-(1,3-benzodioxol-5-yl)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]octane

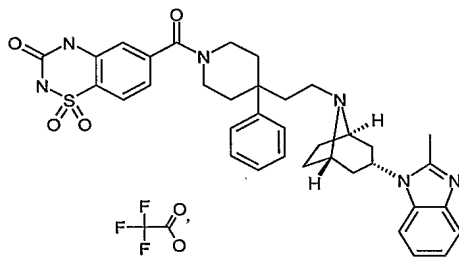


5 ^1H NMR (400 MHz, CDCl_3) δ 73.7-7.12 (m, 9H), 6.67-6.63 (m, 2H), 5.83 (s, 2H), 4.04 (m, 1H), 3.61-3.10 (m, 5H), 2.89 (m, 1H), 2.41-2.17 (m, 3H), 2.10-1.82 (m, 6H), 1.71 (m, 1H), 1.64-1.46 (m, 4H), 1.36-1.28 (m, 2H), 1.19 (m, 2H). HRMS (M+H) calc: 523.2961, found 523.2957, delta 0.4 mmu.

10

Example 791

6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-2H-1,2,4-benzothiadiazin-3(4H)-one 1,1-dioxide



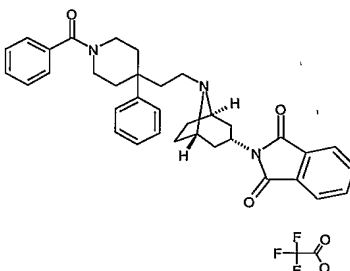
15

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.17 (s, 1H), 7.84-7.69 (m, 3H), 7.65-7.56 (m, 1H), 7.51-7.36 (m, 6H), 7.3-7.17 (m, 2H), 5.15 (m, 1H), 4.34-3.84 (m, 5H), 3.27 (m, 2H), 2.81-2.71 (m, 5H), 2.62 (m, 2H), 2.54-2.50 (m, 2H), 2.25-2.11 (m, 8H), 1.86 (m, 2H). MS (electrospray +) 653.18 (M+1).

539

Example 792

2-[(1R,5S)-8-[2-(1-benzoyl-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl]-1H-isoindole-1,3(2H)-dione

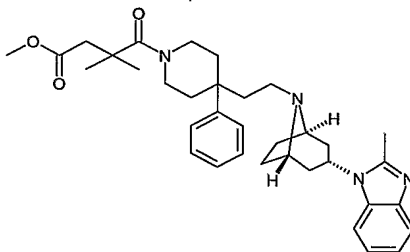


5 ^1H NMR (500 MHz, DMSO- d_6) δ 7.80 (s, 4H), 7.43-7.33 (m, 9H), 7.21 (m, 1H), 4.31 (m, 1H), 4.07 (m, 1H), 3.88 (m, 1H), 3.13 (m, 3H), 2.50 (s, 2H), 2.18-1.98 (m, 4H), 1.80-1.66 (m, 9H), 1.42-1.36 (m, 2H).
HRMS (M+H) calc: 548.2913, found 548.2900, delta 1.3 mmu.

10

Example 793

methyl 3,3-dimethyl-4-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-4-oxobutanoate

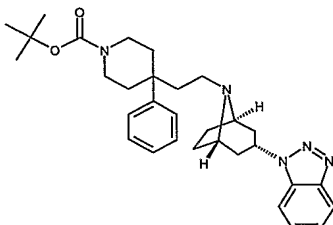


15 ^1H NMR (400 MHz, CDCl_3) δ 7.61 (m, 1H), 7.32-7.05 (m, 8H), 4.62-4.52 (m, 1H), 4.10-3.99 (m, 1H), 3.89-3.82 (m, 2H), 3.59 (m, 4H), 2.51 (m, 5H), 2.31 (m, 2H), 2.17 (m, 1H), 1.91-1.70 (m, 9H), 1.54 (m, 2H), 1.18 (m, 6H). HRMS (M+H) calc: 571.3646, found 571.3666, delta 1.8 mmu.

540

Example 794

tert-butyl 4-{2-[(1R,5S)-3-(1H-1,2,3-benzotriazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidine-1-carboxylate

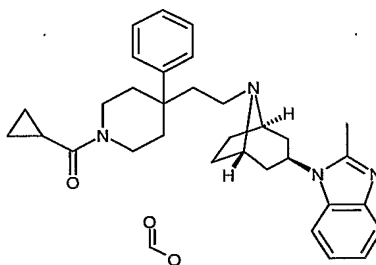


¹H NMR (300 MHz, CDCl₃) δ 7.95 (m, 1H), 7.43-7.08 (m, 8H), 4.78 (m, 1H), 3.62-3.57 (m, 2H), 3.17-3.08 (m, 4H), 2.46-2.34 (m, 2H), 2.27-2.18 (m, 2H), 2.12-1.92 (m, 4H), 1.81-1.54 (m, 8H), 1.38 (s, 9H).

HRMS (M+H) calc: 516.3339, found 516.3336, delta 0.2 mmu.

Example 795

1-((1R,5S)-8-{2-[1-(cyclopropylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

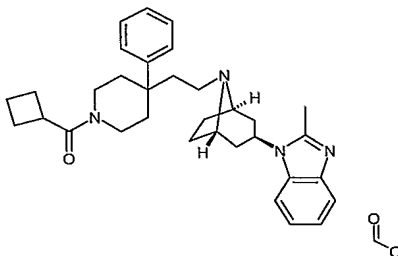


¹H NMR (400 MHz, methanol-d₄) δ 7.92 (m, 1H), 7.55-7.39 (m, 5H), 7.31-7.16 (m, 3H), 4.71 (m, 1H), 4.09-3.95 (m, 4H), 3.52-3.39 (m, 1H), 3.29-3.07 (m, 2H), 2.88-2.74 (m, 4H), 2.65 (s, 3H), 2.39-1.73 (m, 12H), 0.83-0.74 (m, 4H). HRMS (M+H) calc: 497.3280, found 497.3286, delta 0.6 mmu.

541

Example 796

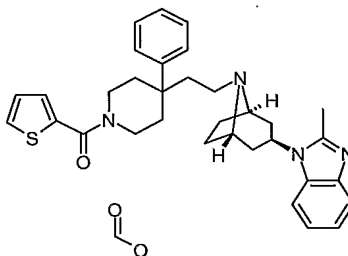
1-((1R,5S)-8-{2-[1-(cyclobutylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



¹H NMR (400 MHz, methanol-d₄) δ 8.28 (s, 1H), 7.50-7.38 (m, 5H), 7.29-7.13 (m, 3H), 4.69 (m, 1H), 4.10-3.93 (m, 3H), 3.62-3.57 (m, 1H), 3.37-3.04 (m, 4H), 2.86-2.66 (m, 4H), 2.60 (s, 3H), 2.26-1.89 (m, 14H), 1.77-1.70 (m, 3H). HRMS (M+H) calc: 511.3437, found 511.3434, delta 0.6 mmu.

Example 797

2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(thien-2-ylcarbonyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole

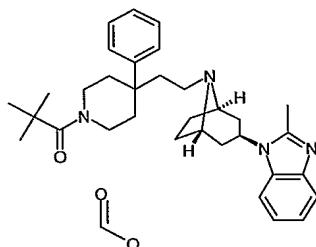


¹H NMR (300 MHz, methanol-d₄) δ 7.96 (m, 1H), 7.62-7.59 (m, 1H), 7.52-7.17 (m, 9H), 7.10 (m, 1H), 4.73 (m, 1H), 4.06 (m, 4H), 3.49-3.36 (m, 2H), 2.90-2.73 (m, 4H), 2.64 (s, 3H), 2.38-1.91 (m, 12H). HRMS (M+H) calc: 539.2845, found 539.2854, delta 0.9 mmu.

542

Example 798

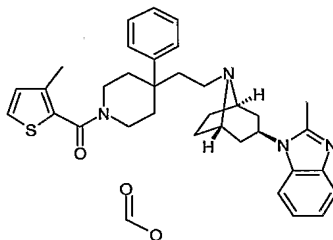
1-((1R,5S)-8-{2-[1-(2,2-dimethylpropanoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole



¹H NMR (400 MHz, methanol-d₄) δ 7.84 (m, 1H), 7.56-7.40 (m, 5H), 7.32-7.26 (m, 1H), 7.20 (m, 2H), 4.73 (m, 1H), 4.03 (m, 3H), 3.30-3.20 (m, 3H), 2.85-2.74 (m, 4H), 2.64 (s, 3H), 2.32-2.29 (m, 2H), 2.20-2.11 (m, 4H), 2.03 (m, 4H), 1.87-1.82 (m, 3H), 1.27 (s, 9H). HRMS (M+H) calc: 513.3593, found 513.3607, delta 1.3 mmu.

Example 799

2-methyl-1-[(1R,5S)-8-(2-{1-[(3-methylthien-2-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole

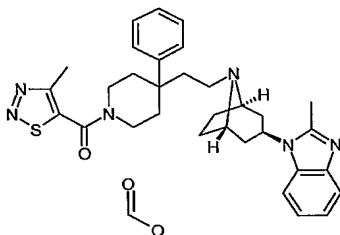


MS (electrospray +) 553 (M+1).

543

Example 800

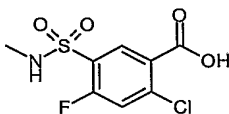
2-methyl-1-[(1R,5S)-8-(2-{1-[(4-methyl-1,2,3-thiadiazol-5-yl)carbonyl]-4-phenyl}piperidin-4-yl)ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



5

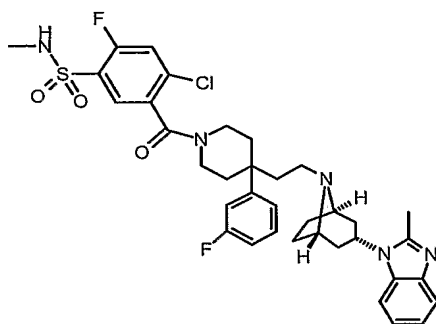
MS (electrospray +) 555 (M+1).

Example 802

Preparation of 2-chloro-4-fluoro-5-[(methylamino)sulfonyl]benzoic acid

20.02g (73.4 mmol) of 2-chloro-3-chlorosulfonyl-4-fluorobenzoic acid was added as a solid to a cooled solution of 10.5 mL of methylamine (40% aqueous solution, 293.6mmol) in 400 mL of water. Reaction was monitored by LC/MS and complete after one hour. The reaction was acidified to pH=1 with concentrated HCl, and solid precipitated out. Product was obtained by filtration. 17.54 g obtained as a pale tan solid (89% yield). ^1H NMR (300 MHz, DMSO- d_6) δ 13.83-14.01 (br, 1 H), 8.21-8.26 (d, 1 H, $J=9.11$ Hz), 7.98-8.03 (q, 1 H, $J=4.82$), 7.88-7.92 (d, 1 H, $J=9.11$ Hz), 2.55-2.56 (d, 3 H, $J=4.82$ Hz).

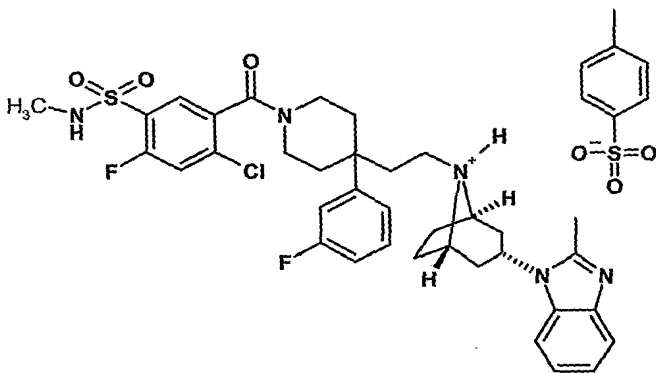
Preparation of 4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methylbenzenesulfonamide



5.36g (12.0 mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole, 3.20 g (12.0 mmol) 2-chloro-4-fluoro-5-[(methylamino)sulfonyl]benzoic acid were combined following the general procedure in Example 5. 3.97 g recovered (47.6% yield). ^1H NMR (300 MHz, DMSO- d_6) δ 7.96-8.05 (br, 1 H), 7.75-7.94 (m, 2

H), 7.38-7.56 (m, 3 H), 7.24-7.30 (m, 2 H), 7.07-7.18 (m, 3 H), 4.48-4.60 (m, 1 H), 3.91-4.03 (m, 1 H), 3.23-3.49 (m, 6 H), 3.04-3.13 (m, 1 H), 2.52-2.60 (m, 4 H), 2.33-2.44 (m, 2 H), 2.12-2.32 (br, 2 H), 2.01-2.09 (m, 2H), 1.76-1.95 (m, 8 H), 1.60-1.66 (m, 2 H). LC/MS m/z (M+H): 696

Preparation of (1*R*,5*S*)-8-{2-[1-{2-chloro-4-fluoro-5-[(methylamino)sulfonyl]benzoyl}-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azoniabicyclo[3.2.1]octane, toluenesulfonic acid salt

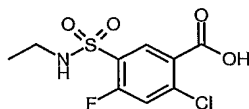


The reaction vessel was charged with (1*R*,5*S*)-8-{2-[1-{2-chloro-4-fluoro-5-[(methylamino)sulfonyl]benzoyl}-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azoniabicyclo[3.2.1]octane (5.0 g) and tetrahydrofuran (65 ml, 13 volumes). The mixture was stirred and heated to 50°C. A solution of toluenesulfonic acid monohydrate (1.4 g, 1 M in tetrahydrofuran, 1 equivalent) was added to the hot mixture. After cooling, the solid was collected by filtration, washed with tetrahydrofuran (2 x 2.5 volumes) and dried *in vacuo*. Yield 93%.

Example 803

Preparation of 2-chloro-5-[(ethylamino)sulfonyl]-4-fluorobenzoic acid

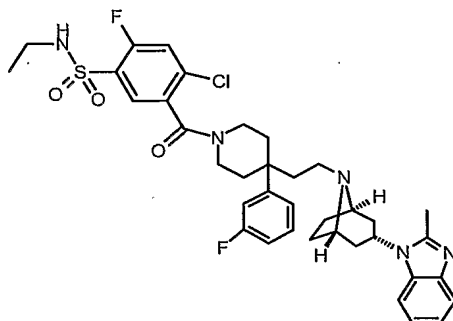
546



1.023 g (3.6 mmol) 3-chlorosulfonyl-4-fluorobenzoic acid was added to 5.49 mL (10.98 mmol) ethylamine in THF. THF was evaporated off at the completion of the reaction. Diluted with dichloromethane and extracted with 6N NaOH. Combined aqueous layers were then acidified to pH=1 with 6N HCl. Product creashes out and is collected by filtration and rinsed with water. Crude product was used in subsequent step without further purification.

^1H NMR (300 MHz, DMSO- d_6) δ 8.13-8.16 (d, 1 H, $J=7.96$ Hz), 8.07-8.11 (t, 1 H, $J=9.79$ Hz), 7.79-7.82 (d, 1 H, $J=9.79$ Hz), 2.86-2.95 (m, 2H), 0.96-1.01 (t, 3 H, $J=7.34$ Hz).

Preparation of 4-chloro-*N*-ethyl-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

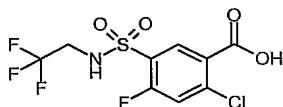


0.103 g (.23 mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and .129 g (.46 mmol) 2-chloro-5-[(ethylamino)sulfonyl]-4-fluorobenzoic acid were combined following the HATU general procedure in Example 5. This compound was purified by flash chromatography on a 0-100% gradient of 1N methanolic ammonia in ethyl acetate in ethyl acetate. 0.76 g obtained (44% yield). ^1H NMR (300 MHz, DMSO- d_6) δ 8.04-8.14 (m, 1 H), 7.86-7.89 (d, 1 H $J=9.83$ Hz), 7.72-7.79 (m, 3 H), 7.41-7.51 (m, 3 H), 7.21-7.26 (m, 2 H), 7.09-7.15 (m, 1 H), 5.00-5.11 (m, 1 H), 4.03-4.14 (m, 2 H), 3.87-3.99 (m, 1 H), 3.19-3.38 (m, 2 H), 2.96-3.05 (m, 1 H), 2.85-2.94 (m, 3 H), 2.69-2.80 (m, 4 H), 2.51-2.64 (m,

2 H), 1.93-2.26 (m, 11 H), 1.73-1.88 (m, 2H), 0.94-1.12 (m, 3H). LC/MS m/z (M+H): 710.

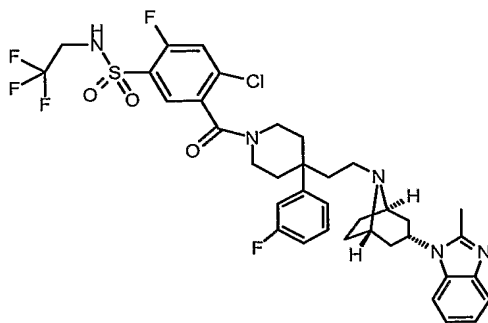
Example 804

Preparation of 2-chloro-4-fluoro-5-[(2,2,2-trifluoroethyl)amino]sulfonyl}benzoic acid



4.997 g (18.3 mmol) 3-chlorosulfonyl-4-fluorobenzoic acid, 2.90 g (27.5 mmol) NaHCO_3 were dissolved in 50 mL water. 1.45 mL (18.3 mmol) trifluoroethylamine was added dropwise to solution. Solution was acidified to pH=1 with concentrated HCl and product was extracted into ethyl acetate. Dried over MgSO_4 and concentrated. 5.27 g recovered (83% yield). Crude product was used in subsequent step without further purification. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.22-9.37 (dt, 1 H, $J=6.44, 30.24$ Hz), 7.80-7.92 (dd, 1 H, $J=9.91, 25.78$ Hz), 4.04-4.16 (m, 1H), 3.77-3.90 (m, 1 H).

Preparation of 4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-(2,2,2-trifluoroethyl)benzenesulfonamide

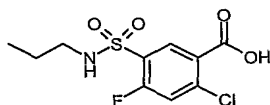


8.792 g (19.7mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and 6.59 g (19.7 mmol) 2-chloro-5-[(2,2,2-trifluoroethylamino)sulfonyl]-4-fluorobenzoic acid were combined following the HATU general procedure in Example 5. This

compound was purified by flash chromatography on a 0-100% gradient of 1N methanolic ammonia in ethyl acetate in ethyl acetate. 6.31 g obtained (42% yield). ^1H NMR (300 MHz, DMSO- d_6) δ 9.18-9.25 (br, 1 H), 7.75-7.94 (m, 2 H), 7.35-7.52 (m, 3 H), 7.22-7.28 (m, 2 H), 7.04-7.15 (m, 3 H), 4.45-4.56 (m, 1 H), 3.80-4.00 (m, 3 H), 3.20-3.43 (m, 6 H), 2.99-3.07 (m, 1 H), 2.48-2.52 (m, 3 H), 2.32-2.41 (m, 2 H), 1.97-2.29 (br, 2 H), 1.74-1.91 (m, 8 H), 1.59-1.64 (m, 2 H).

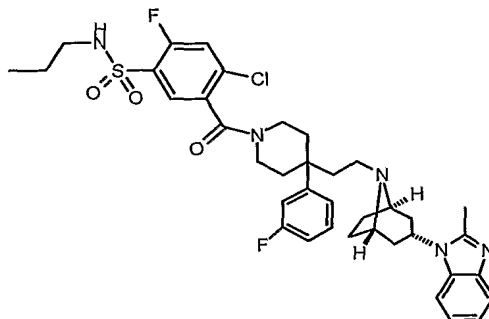
Example 805

Preparation of 2-chloro-4-fluoro-5-[(propylamino)sulfonyl]benzoic acid



2.512 g (9.2 mmol) 3-chlorosulfonyl-4-fluorobenzoic acid was added to 2.27 mL (27.6 mmol) propylamine following the general procedure in for 2-chloro-5-[(ethylamino)sulfonyl]-4-fluorobenzoic acid. Crude product was used in subsequent step without further purification. ^1H NMR (300 MHz, DMSO- d_6) δ 8.19-8.22 (d, 1 H, J = 7.84 Hz), 8.12-8.16 (t, 1 H, J =11.59 Hz), 7.85-7.88 (d, 1 H, J =9.90 Hz), 2.80-2.87 (q, 2 H, J =6.82), 1.33-1.45 (m, 2 H), 0.77-0.82 (t, 3 H, J =7.51 Hz).

Preparation of 4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-propylbenzenesulfonamide

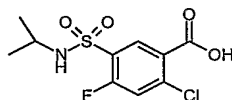


0.366 g (0.82 mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and 0.363 g (1.23 mmol) 2-chloro-4-fluoro-5-[(propylamino)sulfonyl]benzoic acid were combined following the HATU general procedure in Example 5. This compound was purified by flash chromatography on a 0-100% gradient of 90:5:5 acetonitrile: ammonium hydroxide: water in acetonitrile. 0.24 g obtained (40% yield).

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.04-8.15 (br, 1 H), 7.69-7.90 (m, 2 H), 7.32-7.52 (m, 3 H), 7.19-7.26 (m, 2 H), 7.01-7.15 (m, 3 H), 4.41-4.56 (m, 1 H), 3.86-3.98 (m, 1 H), 3.19-3.43 (m, 6 H), 2.97-3.08 (m, 1 H), 2.77-2.88 (m, 2 H), 2.44 (s, 3H), 2.28-2.41 (m, 2 H), 1.96-2.17 (m, 2H), 1.71-1.92 (m, 9 H), 1.56-1.64 (m, 2 H), 1.31-1.42 (m, 2 H), 0.73-0.81 (m, 3 H).

Example 806

Preparation of 2-chloro-4-fluoro-5-[(isopropylamino)sulfonyl]benzoic acid

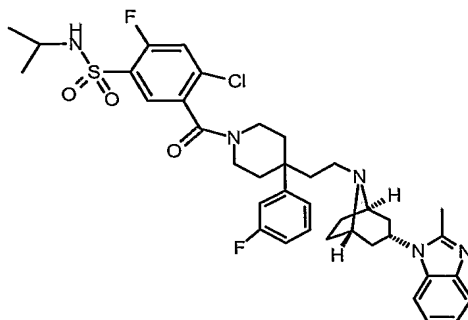


1.002 g (3.6 mmol) 3-chlorosulfonyl-4-fluorobenzoic acid was added to 0.94 mL (10.9 mmol) isopropylamine following the general procedure in for 2-chloro-5-[(ethylamino)sulfonyl]-4-fluorobenzoic acid. Crude product was used in subsequent step without further purification

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.20-8.23 (d, 1 H, *J*=8.28 Hz), 8.12-8.17 (t, 1 H, *J*=7.30 Hz), 7.83-7.87 (d, 1 H, *J*=10.23 Hz), 3.30-3.43 (m, 1H), 0.98-1.01 (d, 6 H, *J*=6.34 Hz).

Preparation of 4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-isopropylbenzenesulfonamide

550

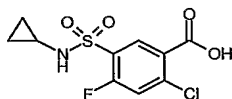


0.290 g (0.65 mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and 0.288 g (0.975 mmol) 2-chloro-4-fluoro-5-[(isopropylamino)sulfonyl]benzoic acid were combined following the HATU general procedure in Example 5. This compound was purified by reverse phase chromatography on a 0-100% gradient of 0.1% TFA in water in acetonitrile. 0.196 g obtained (42% yield).

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.09-8.19 (m, 1 H), 7.76-7.99 (m, 2 H), 7.38-7.55 (m, 4 H), 7.25-7.31 (m, 1 H), 7.07-7.20 (m, 3 H), 4.52-4.62 (m, 1 H), 3.92-4.01 (m, 1 H), 3.29-3.43 (m, 6 H), 3.01-3.11 (m, 1 H), 2.76 (s, 1 H), 2.47-2.51 (m, 2 H), 2.36-2.45 (m, 1 H), 1.78-2.04 (m, 12 H), 1.25-1.32 (m, 3H), 0.99-1.07 (m, 6H).

Example 807

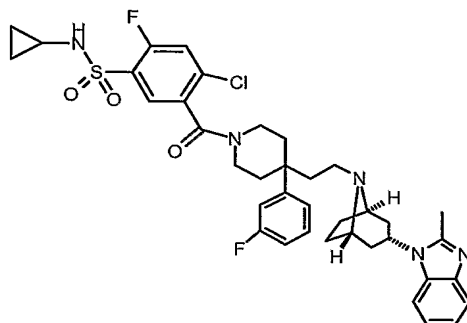
Preparation of 2-chloro-5-[(cyclopropylamino)sulfonyl]-4-fluorobenzoic acid



1.005 g (3.6 mmol) 3-chlorosulfonyl-4-fluorobenzoic acid was added to 0.76 mL (10.9 mmol) cyclopropylamine following the general procedure in for 2-chloro-5-[(ethylamino)sulfonyl]-4-fluorobenzoic acid. Crude product was used in subsequent step without further purification

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.46-8.48 (d, 1 H, *J* = 2.83 Hz), 8.22-8.26 (d, 1 H, *J* = 7.69 Hz), 7.86-7.90 (d, 1 H, *J* = 9.70), 2.23-2.32 (m, 1 H), 0.46-0.56 (m, 2 H), 0.36-0.44 (m, 2 H).

Preparation of 4-chloro-N-cyclopropyl-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

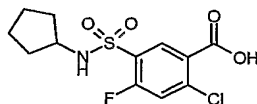


0.335 g (0.75 mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and 0.242 g (0.83 mmol) 2-chloro-4-fluoro-5-[(cyclopropylamino)sulfonyl]benzoic acid were combined following the HATU general procedure in Example 5. This compound was purified by reverse phase chromatography on a 0-100% gradient of 0.1% TFA in water in acetonitrile. 0.231 g obtained (43% yield).

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.38-8.47 (br, 1 H), 7.72-7.92 (m, 2 H), 7.33-7.51 (m, 3 H), 7.20-7.28 (m, 2 H), 7.01-7.16 (m, 3 H), 4.45-4.57 (m, 1 H), 4.06-4.12 (m, 1 H), 3.87-3.98 (m, 1 H), 3.21-3.42 (m, 6 H), 2.97-3.10 (m, 1 H), 2.44 (s, 3 H), 2.23-2.42 (m, 2 H), 1.95-2.17 (m, 2 H), 1.72-1.92 (m, 8 H), 1.55-1.65 (m, 2 H), 0.34-0.53 (m, 4 H).

Example 808

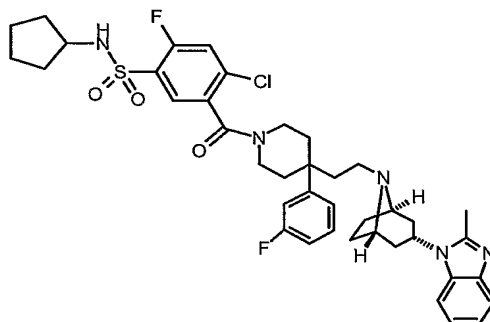
Preparation of 2-chloro-5-[(cyclopentylamino)sulfonyl]-4-fluorobenzoic acid



1.01 g (3.7 mmol) 3-chlorosulfonyl-4-fluorobenzoic acid was added to 1.08 mL (10.9 mmol) cyclopentylamine following the general procedure in for 2-chloro-5-[(ethylamino)sulfonyl]-4-fluorobenzoic acid. Crude product was used in subsequent step without further purification

^1H NMR (300 MHz, DMSO- d_6) δ 8.21-8.24 (m, 2 H), 7.84-7.88 (d, 1 H, $J=10.14$ Hz), ..48-3.59 (m, 1 H), 1.48-1.70 (m, 4 H), 1.28-1.46 (m, 4 H).

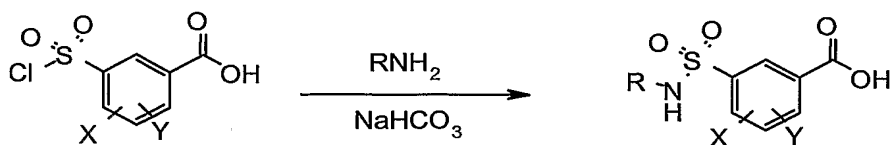
Preparation of 4-chloro-N-cyclopentyl-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



0.103 g (0.23 mmol) 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and 0.148 g (0.46 mmol) 2-chloro-4-fluoro-5-[(cyclopentylamino)sulfonyl]benzoic acid were combined following the HATU general procedure in Example 5. This compound was purified by reverse phase chromatography on a 0-100% gradient of 0.1% TFA in water in acetonitrile. 0.068 g obtained (40% yield).

^1H NMR (300 MHz, DMSO- d_6) δ 9.32-9.49 (br, 1 H), 8.13-8.25 (m, 2 H), 7.73-7.91 (m, 3 H), 7.39-7.56 (m, 2 H), 7.08-7.30 (m, 3 H), 5.00-5.15 (m, 1 H), 4.03-4.16 (m, 2 H), 3.83-4.02 (m, 1 H), 3.35-3.58 (m, 2 H), 3.19-3.33 (m, 2 H), 3.16 (s, 1 H), 2.94-3.08 (m, 2 H), 2.67-2.80 (m, 6 H), 2.54-2.65 (m, 1 H), 2.02-2.26 (m, 8H), 1.72-2.01 (m, 2 H), 1.47-1.67 (m, 4H), 1.26-1.44 (m, 4 H)

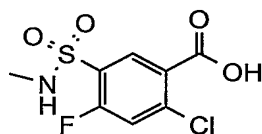
(Alkyl- or alkoxy-amino)benzoic Acids listed below were prepared using the following scheme



R= methyl, ethyl, propyl, isopropyl, cyclopropyl
cyclopentyl, methoxy, ethoxy, etc.

X, Y = Cl, F,

Preparation of 2-Chloro-4-Fluoro-5-[(Methylamino)sulfonyl]benzoic Acid



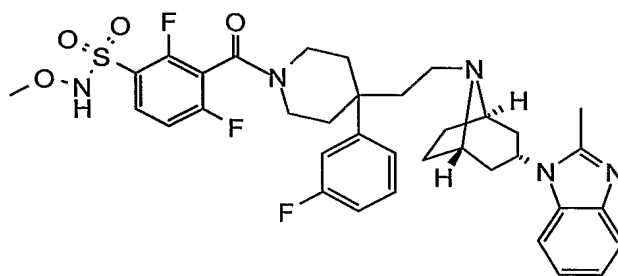
At 0 °C, to a stirred ice-water suspension (~200 mL) of 2-chloro-5-(chlorosulfonyl)-4-fluorobenzoic acid was slowly added a precooled 40% methylamine (13 mL). The reaction mixture was then stirred for 2 hours before being acidified to pH~2. The desired product was precipitated and filtered out. After being dried overnight, the pure 2-chloro-4-fluoro-5-[(methylamino)sulfonyl]benzoic acid was obtained as white solid (9.8g, 100%).

The corresponding substituted aminosulfonyl benzoic acids used in this patent were prepared in the similar methods as described above.

Example 809

Preparation of 2,4-Difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-N-methoxybenzenesulfonamide

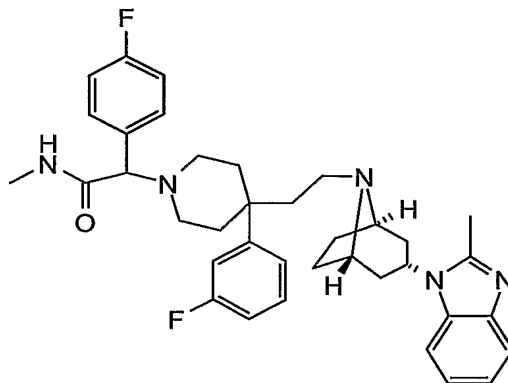
554



2,4-Difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methoxybenzenesulfonamide (11mg, 17%) was obtained as solid from 3-(chlorosulfonyl)-2,6-difluorobenzoic acid (105 mg, 0.4 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (52 mg, 0.1 mmol) and methoxyamine hydrochloride (33mg, 0.4 mmol) following the coupling procedure in example 473. ¹H NMR (400 MHz, CD₃OD), δ 8.04 (q, *J*=3.3 Hz, 1 H), 7.97 (s, 2 H), 7.53 (d, *J*=9.6 Hz, 1 H), 7.45-7.40 (m, 2 H), 7.36-7.16 (m, 4, H), 7.01 (t, *J*=6.8 Hz, 1 H), 4.80-4.71 (m, 1 H), 4.20-4.19 (br, 1 H), 3.74 (d, *J*=10.1 Hz, 3 H), 3.57-3.42 (m, 4 H), 3.30-3.27 (m, 1 H), 2.54 (s, 3 H), 2.51-2.25 (m, 4 H), 2.09-1.93 (m, 10 H), 1.75 (d, *J*=7.6 Hz, 2 H). HRMS *m/z* (*M*+*H*)⁺ calcd: 696.2831, obsd: 696.2831.

Example 810

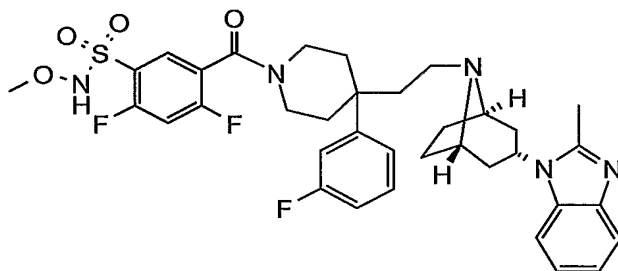
Preparation of 2-(4-fluorophenyl)-2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-*N*-methylacetamide



(4-Fluorophenyl)(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetic acid (prepared from 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole and 4-fluorophenylboronic acid following the procedure outlined in example 412. (19 mg, 0.032 mmol) was coupled with methylamine (16 μ L, 2M in THF) under promotion of HATU (12 mg, 0.032mmol) The title compound was obtained as solid (12mg, 60%) after purification by flash chromatography, eluting with a gradient of 0-10%methanol in ethyl acetate. ^1H NMR (400 MHz, CDCl_3) δ 7.66 (d, $J=7.1$ Hz, 1 H), 7.32-7.24 (m, 4 H), 7.19-7.12 (m, 2 H), 7.03-6.89 (m, 6H), 4.59 (br, 1 H), 3.75 (s, 1 H), 3.22 (br, 2 H), 2.84 (d, $J=4.9$ Hz, 3 H), 2.55 (s, 3 H), 2.52-2.47 (m, 1 H), 2.40-2.09 (m, 6 H), 1.93-1.87 (m, 7 H), 1.78-1.61 (m, 6 H). HRMS m/z ($M+H$) $^+$ calcd 612.3514, obsd 612.3530.

Example 811

Preparation of 2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methoxybenzenesulfonamide

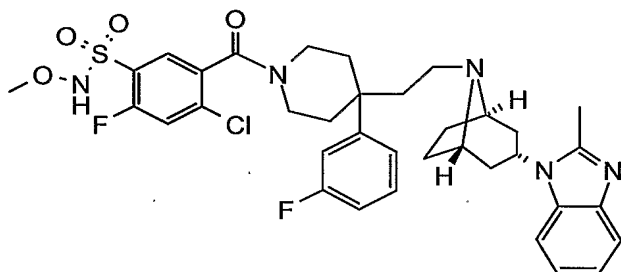


2,4-Difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methoxybenzene sulfonamide (119 mg, 43%) was obtained as solid from 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-

benzimidazole dihydrochloride (244mg, 0.4 mmol) and 2,4-difluoro-5-[(methoxyamino)sulfonyl]benzoic acid (266mg, 1 mmol) and HATU (152 mg, 0.4 mmol), following the coupling procedure in example 5. ^1H NMR (400 MHz, CDCl_3) δ 7.66 (d, $J=7.3$ Hz, 1 H), 7.40-7.34 (m, 1 H), 7.0 (d, $J=7.3$ Hz, 1 H), 7.21-7.14 (m, 2 H), 7.04-6.96 (m, 5H), 4.65-4.60 (m, 1 H), 4.23-4.20 (m, 1 H), 3.80 (s, 3 H), 3.34-3.24 (m, 6 H), 2.58 (s, 3 H), 2.45-2.37 (m, 2 H), 2.34-2.14 (m, 2 H), 2.07-1.77 (m, 12 H). HRMS m/z ($\text{M}+\text{H}$) $^+$ calcd 696.2831, obsd 696.2812.

Example 812

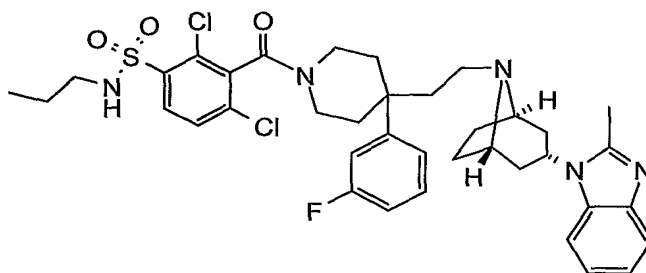
Preparation of 4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methoxybenzenesulfonamide



4-Chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methoxybenzenesulfonamide (170 mg, 60%) was obtained as solid from 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (244 mg, 0.4 mmol) and 2-chloro-4-fluoro-5-[(methoxyamino)sulfonyl]benzoic acid (283mg, 1 mmol) and HATU (152 mg, 0.4 mmol), following the procedures outlined in example 5. ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, $J=7.2$ Hz, $\frac{1}{2}$ H, rotamer), 7.76 (d, $J=7.1$ Hz, $\frac{1}{2}$ H, rotamer), 7.63 (d, $J=7.5$ Hz, 1 H), 7.38-7.28 (m, 3 H), 7.18-7.12 (m, 2 H), 7.08-7.04 (m, 1 H), 6.98-6.94 (m, 2 H), 4.62-4.57 (m, 1 H), 4.26-4.17 (m, 1 H), 3.78 (d, $J=9.9$ Hz, 3 H), 3.42-3.10 (m, 6 H), 2.55 (s, $\frac{3}{2}$ H, rotamer), 2.54 (s, $\frac{3}{2}$ H, rotamer), 2.42-2.32 (m, 3 H), 2.14-2.07 (m, 1 H), 1.94-1.70 (m, 10 H), 1.64-1.63 (m, 2 H). HRMS m/z ($\text{M}+\text{H}$) $^+$ calcd 712.2536, obsd 712.2546.

Example 813

Preparation of 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-propylbenzenesulfonamide

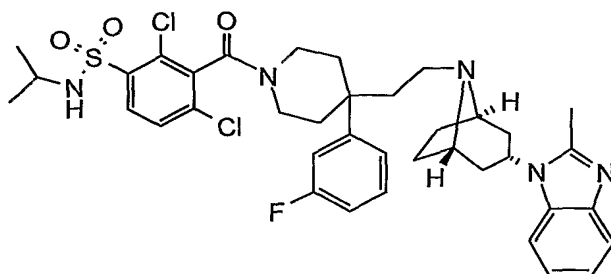


2,4-Dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-propylbenzenesulfonamide (11 mg, 15%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (58 mg, 0.2 mmol), propyl amine (20 μ L, 0.2mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (61 mg, 0.1 mmol) following the procedure outlined in example 473. ^1H NMR (400 MHz, CD_2Cl_2), δ 8.06=8.01 (m, 1 H), 7.59-7.48 (m, 2 H), 7.42-7.34 (m, 2 H), 7.20-7.16 (m, 3 H), 7.14-6.96 (m, 2 H), 4.68 (br, 1 H), 4.23-4.20 (m, 1 H), 3.47-3.13 (m, 6 H), 2.96-2.82 (m, 4), 2.53 (s, 3/2 H), 2.41 (s, 3/2 H), 2.36-2.16 (m, 5 H), 1.98-1.84 (m, 7 h), 1.68-1.61 (m, 2 H), 1.52-1.44 (m, 2 H), 0.90-0.86 (m, 3 H). HRMS m/z ($\text{M}+\text{H}$) $^+$ calcd: 740.2604, obsd: 740.2589.

Example 814

Preparation of 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-isopropylbenzenesulfonamide

558

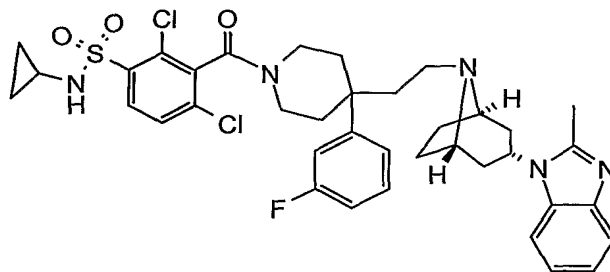


2,4-Dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-isopropylbenzene

sulfonamide (13.5 mg, 18%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (58 mg, 0.2 mmol), isopropyl amine (20 μ L, 0.2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (61 mg, 0.1 mmol) following the procedure outlined in example 473. ^1H NMR (400 MHz, CD_2Cl_2), δ 8.07 (d, $J=8.6$ Hz, 1 H), 7.58-7.50 (m, 2 H), 7.42-7.35 (m, 2 H), 7.21-7.12 (m, 2 H), 7.06-6.95 (m, 3 H), 4.70-4.65 (m, 1 H), 4.23-4.19 (m, 1 H), 3.47-3.27 (m, 5 H), 3.22-3.14 (m, 2 H), 2.53 (s, 3 H), 2.46-2.32 (m, 3 H), 2.16 (br, 1 H), 1.98-1.83 (m, 11 H), 1.68 (d, $J=7.7$ Hz, 2 H), 1.25-1.03 (m, 6 H). HRMS m/z ($M+H$) $^+$ calcd: 740.2604, obsd: 740.2590.

Example 815

Preparation of 2,4-dichloro-*N*-cyclopropyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

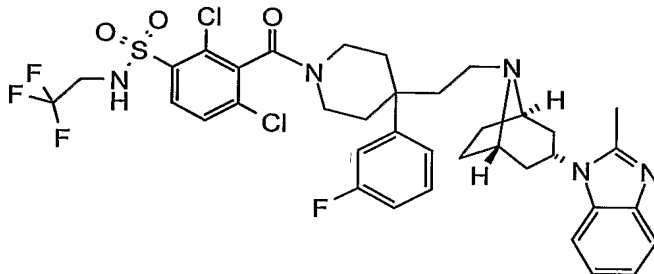


2,4-Dichloro-*N*-cyclopropyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzene

sulfonamide (12 mg, 15%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (58 mg, 0.2 mmol), cyclopropyl amine (17 μ L, 0.2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (61 mg, 0.1 mmol) following the procedure outlined in example 473. ^1H NMR (400 MHz, CD_2Cl_2), δ 8.10 (d, $J=7.6$ Hz, 1 H), 7.59-7.52 (m, 2 H), 7.42-7.36 (m, 2 H), 7.19-7.12 (m, 3 H), 7.07-6.97 (m, 2 H), 4.67-4.63 (m, 1 H), 4.24-4.20 (m, 1 H), 3.49-3.14 (m, 6 H), 2.53 (s, 3 H), 2.44-2.33 (m, 3 H), 2.12 (br, 1 H), 1.96-1.85 (m, 11 H), 1.67-1.65 (m, 2 H), 0.74-0.67 (m, 1 H), 0.61-0.51 (m, 3 H). HRMS m/z ($\text{M}+\text{H}$) $^+$ calcd: 738.2448, obsd: 738.2433.

Example 816

Preparation of 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-(2,2,2-trifluoroethyl)benzenesulfonamide

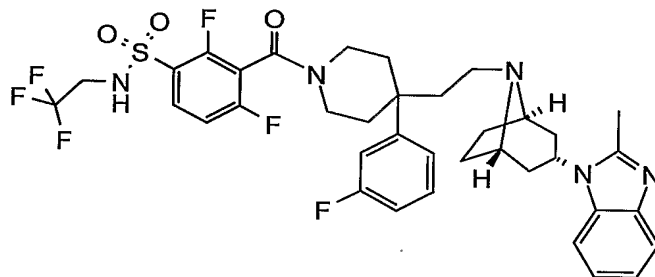


2,4-Dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-(2,2,2-trifluoroethyl)benzenesulfonamide (220 mg, 56%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (290 mg, 1 mmol), 2,2,2-trifluoroethylamine (160 μ L, 2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5 mmol) following the procedure outlined in example 473. ^1H NMR (400

MHz, CD₂Cl₂), δ 8.03 (d, J =8.4 Hz, 1 H), 7.59-7.54 (m, 1 H), 7.562-7.47 (m, 1 H), 7.42-7.34 (m, 2 H), 7.19-7.12 (m, 3 H), 7.06-6.96 (m, 2 H), 4.65-4.60 (m, 1 H), 4.22-4.18 (m, 1 H), 3.79-3.69 (m, 2 H), 3.48-3.45 (m, 1 H), 3.27-3.12 (m, 3 H), 3.11-3.05 (m, 1 H), 2.52 (s, 3 H), 2.43-2.30 (m, 3 H), 2.19-2.16 (m, 2 H), 1.97-1.81 (m, 10 H), 1.66-1.62 (m, 2 H). HRMS m/z (M+H)⁺ calcd: 780.2165, obsd: 780.2164.

Example 817

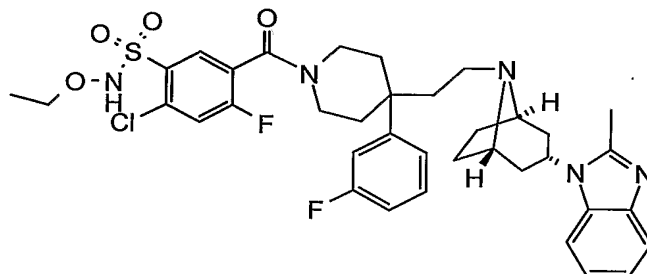
Preparation of 2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-(2,2,2-trifluoroethyl)benzenesulfonamide



2,4-Difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-(2,2,2-trifluoroethyl)benzenesulfonamide (260 mg, 70 %) was obtained as solid from 2,6-difluoro-3-(chlorosulfonyl)benzoic acid (260 mg, 1 mmol), 2,2,2-trifluoroethylamine (160 μ L, 2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5 mmol) following the procedure outlined in example 473. ¹H NMR (400 MHz, CD₂Cl₂), δ 7.98-7.92 (m, 1 H), 7.60-7.58 (m, 1 H), 7.41-7.32 (m, 2 H), 7.22-7.20 (m, 2 H), 7.16-6.98 (m, 4 H), 4.69-4.67 (m, 1 H), 4.18 (br, 1 H), 3.80-3.62 (m, 1 H), 3.45-3.39 (m, 3 H), 3.25-3.20 (m, 1 H), 2.55 (s, 3 H), 2.402-2.42 (m, 2 H), 2.42-2.40 (m, 1 H), 2.32-1.83 (m, 212 H), 1.73-1.38 (m, 2 H). HRMS m/z (M+H)⁺ calcd: 748.2756, obsd: 748.2759.

Example 818

Preparation of 2-chloro-*N*-ethoxy-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

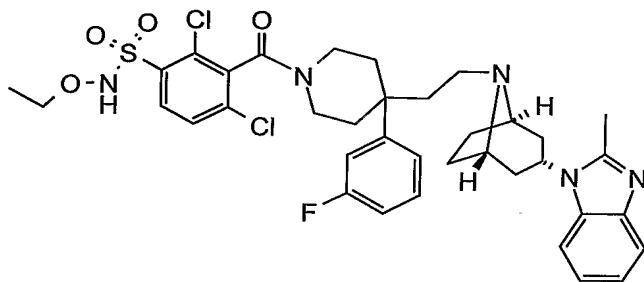


2-Chloro-*N*-ethoxy-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide (60 mg, 16%) was obtained as solid from 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5mmol) and 2-fluoro-4-chloro-5-[(ethoxyamino)sulfonyl]benzoic acid (297mg, 1 mmol) and HATU (190 mg, 0.5 mmol), following the procedures outlined in example 5. ¹H NMR (400 MHz, CD₂Cl₂) δ 8.15 (br, 1 H), 7.59-7.57 (m, 1 H), 7.42-7.35 (m, 3 H), 7.16-7.12 (m, 3 H), 7.07-6.97 (m, 2 H), 4.64-4.60 (m, 1 H), 4.15-4.01 (m, 4 H), 3.42-3.19 (m, 5 H), 2.53 (s, 3 H), 2.43-2.32 (m, 3 H), 2.18-2.11 (m, 1 H), 1.96-1.83 (m, 10 H), 1.66-1.64 (m, 2 H), 1.17 (t, J=6.9 Hz, 3 H). HRMS *m/z* (M+H)⁺ calcd 726.2692, obsd 726.2704.

Example 819

Preparation of 2,4-dichloro-*N*-ethoxy-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

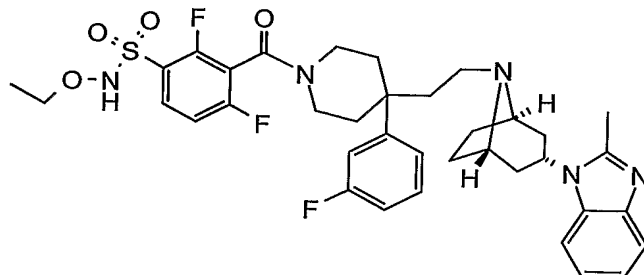
562



2,4-Dichloro-*N*-ethoxy-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide (22.5 mg, 6%) was obtained as solid from 2,6-dichloro-3-(chlorosulfonyl)benzoic acid (290 mg, 1 mmol), ethoxyamine hydrochloride (195 mg, 2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5 mmol) following the procedure outlined in example 473. ¹H NMR (400 MHz, CD₂Cl₂), δ 8.10-8.08 (m, 1 H), 7.60-7.55 (m, 2 H), 7.40-7.35 (m, 2 H), 7.18-7.12 (m, 3 H), 7.07-6.96 (m, 2 H), 4.65-4.60 (m, 2 H), 4.23-4.20 (m, 1 H), 4.06-4.00 (m, 2 H), 3.34-3.12 (m, 6 H), 2.54-2.53 (m, 2 H), 2.44-2.44 (m, 4 H), 2.20-2.03 (m, 2 H), 1.97-1.84 (m, 12 H), 1.65 (d, *J*=7.9 Hz, 2 H), 1.18-1.14 (m, 3 H). HRMS *m/z* (*M*+*H*)⁺ calcd: 742.2397, obsd: 742.2424.

Example 820

Preparation of *N*-ethoxy-2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

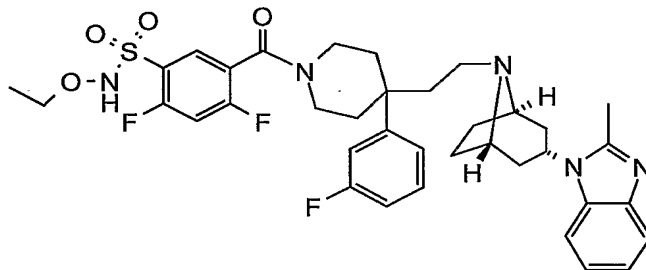


N-ethoxy-2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzene

sulfonamide (27.9mg, 8%) was obtained as solid from 2,6-difluoro-3-(chlorosulfonyl)benzoic acid (260 mg, 1 mmol), ethoxyamine hydrichloride (195 mg, 2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5 mmol) following the procedure outlined in example 473. ¹H NMR (400 MHz, CD₂Cl₂), δ 8.00-7.95 (m, 1 H), 7.58-7.56 (m, 1 H), 7.42-7.35 (m, 2 H), 7.17-7.10 (m, 4 H), 7.06-6.97 (m, 2 H), 4.65-4.60 (m, 1 H), 4.21-4.00 (m, 3 H), 3.43-3.19 (m, 5 H), 2.53 (s, 3 H), 2.44-2.32 (m, 4 H), 2.17-2.15 (m, 1 H), 1.97-1.80 (m, 10 H), 1.65 (d, J=7.8 Hz, 2 H), 1.18-1.11 (m, 3 H). HRMS *m/z* (M+H)⁺ calcd: 710.2988, obsd: 710.2975.

Example 821

Preparation of *N*-ethoxy-2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



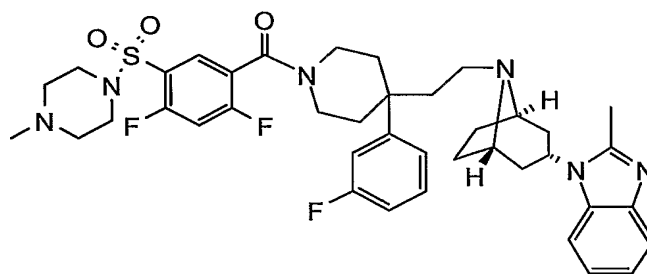
N-ethoxy-2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzene

sulfonamide (25mg, 7%) was obtained as solid from 2,4-difluoro-3-(chlorosulfonyl)benzoic acid (260 mg, 1 mmol), ethoxyamine hydrichloride (195 mg, 2 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5 mmol) following the procedure outlined in example 473. ¹H NMR (400 MHz, CD₂Cl₂), δ 7.96 (br, 1 H), 7.57-7.55 (m, 1 H), 7.42-7.35 (m, 2 H), 7.16-7.11 (m, 3 H), 7.08-6.96 (m, 3 H), 4.65-4.60 (m, 1 H), 4.14-4.03 (m, 3 H), 3.42-3.17 (m, 5 H), 2.52 (s, 3 H), 2.43-2.31 (m, 4), 2.13-2.09 (m, 1 H), 1.98-

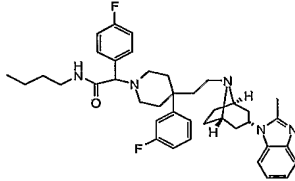
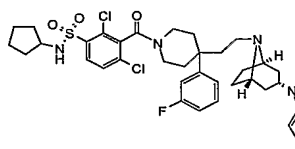
1.80 (m, 10 H), 1.65 (d, $J=7.8$ Hz, 2 H), 1.18 (t, $J=7.0$ Hz, 3 H). HRMS m/z ($M+H$)⁺ calcd: 710.2988, obsd: 710.2975.

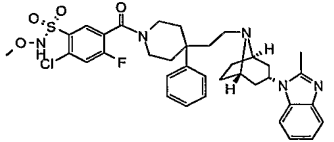
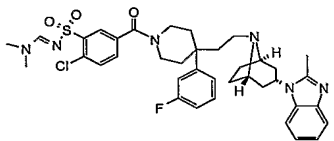
Example 822

Preparation of 1-((1*R*,5*S*)-8-{2-[1-{2,4-difluoro-5-[(4-methylpiperazin-1-yl)sulfonyl]benzoyl}-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole



1-((1*R*,5*S*)-8-{2-[1-{2,4-difluoro-5-[(4-methylpiperazin-1-yl)sulfonyl]benzoyl}-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (170mg, 44%) was obtained as solid from 2-chloro-4-fluoro-5-[(4-methylpiperazin-1-yl)sulfonyl]benzoic acid (170 mg, 0.5 mmol), HATU (190 mg, 0.5 mmol) and 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (305 mg, 0.5 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz, DMSO-*d*₆), δ 7.93-7.88 (m, 1 H), 7.79-7.75 (m, 1 H), 7.47 (d, $J=8.4$ Hz, 1 H), 7.43-7.33 (m, 2 H), 7.23-7.21 (m, 3 H), 7.12-7.04 (m, 3 H), 4.50-4.46 (m, 1 H), 3.93-3.90 (m, 1 H), 3.30 (br, 4 H), 3.16-3.04 (m, 5 H), 2.43(s, 3 H), 2.32(br, 6 H), 2.13-2.12 (m, 4 H), 1.98-1.57 (m, 13 H). HRMS m/z ($M+H$)⁺ calcd: 765.3149, obsd: 765.3165.

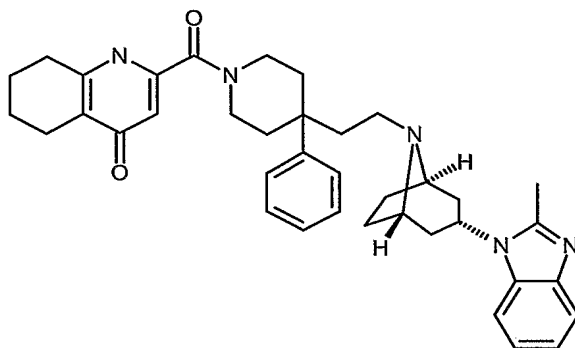
# Example	Structure	^1H NMR (400 MHz, CDCl_3)	HRMS m/z (M+H) $^+$
823		δ 7.66 (d, J=7.1 Hz, 1 H), 7.33-7.24 (m, 4 H), 7.19-7.12 (m, 2 H), 7.04-6.89 (m, 6H), 4.59 (br, 1 H), 3.73 (s, 1 H), 3.29-3.22 (m, 4 H), 2.55 (s, 3 H), 2.52-2.48 (m, 1 H), 2.40-2.10 (m, 6 H), 1.93-1.87 (m, 8 H), 1.79-1.61 (m, 6 H), 1.53-1.46 (m, 2, H), 1.43-1.30 (m, 2 H), 0.92 (t, J=7.3 Hz, 3 H)	Calcd 654.3983, obsd 654.3998.
824		δ 8.06 (d, J=8.4 Hz, 1 H), 7.57-7.50 (m, 2 H), 7.42-7.35 (m, 2 H), 7.20-7.12 (m, 3 H), 7.06-6.96 (m, 2 H), 4.70-4.65 (m, 1 H), 4.22-4.18 (m, 1 H), 3.58-3.12 (m, 6 H), 2.52 (s, 3 H), 2.46-2.36 (m, 3 H), 2.18 (br, 2 H), 1.96-1.83 (m, 11 H), 1.79-1.61 (m, 6 H), 1.47-1.38 (m, 4 H).	calcd: 766.2761, obsd: 766.2776

825		δ 8.18 (br, 1 H), 7.59-7.57 (m, 1 H), 7.43-7.33 (m, 6 H), 7.29-7.25 (m, 1 H), 7.20-7.16 (m, 2 H), 4.67-4.62 (m, 1 H), 4.18-4.15 (m, 1 H), 3.78 (s, 3 H), 3.40-3.31 (m, 4 H), 3.18-3.15 (m, 1H), 2.54 (s, 3 H), 2.46-2.34 (m, 3 H), 2.18-2.02 (m, 1 H) 1.99-1.84 (m, 11 H), 1.68-1.67 (2 H).	calcd 694.2630, obsd 694.2623.
826		δ 8.21 (d, J=10 Hz, 2 H), 7.66 (d, J=10 Hz, 1 H), 7.50 (s, 2 H), 7.35-7.29 (m, 2 H), 7.20-7.13 (m, 2 H), 7.10-6.90 (m, 3 H), 4.60 (br, 1 H), 4.20 (br, 1 H), 3.55 (br, 1 H), 3.40-3.25 (m, 4 H), 3.18 (s, 3 H), 3.04 (s, 3 H), 2.57 (s, 3 H), 2.45-2.35 (m, 2 H), 2.30-2.21 (m, 2 H), 1.95-1.89 (m, 12 H), 1.65-1.63 (m, 2 H).	calcd: 765.3149, obsd: 765.3165.

Example 827Preparation of

2-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny]carbonyl]-5,6,7,8-tetrahydro-4(1*H*)-quinolinone

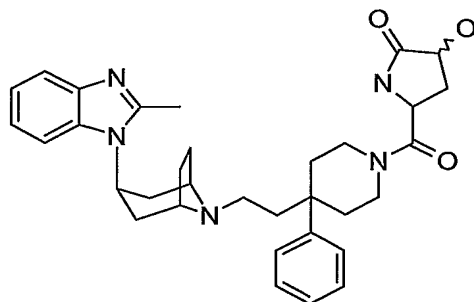
567



2-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny]carbonyl]-5,6,7,8-tetrahydro-4(1*H*)-quinolinone (5.2 mg; 17% yield) was obtained as a solid from 4-oxo-1,4,5,6,7,8-hexahydro-2-quinolinecarboxylic acid (9.66 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny]ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M-H): 602.36.

Example 828

3-hydroxy-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny]carbonyl]-2-pyrrolidinone

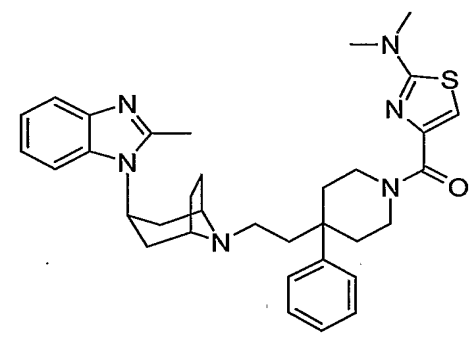


3-hydroxy-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny]carbonyl]-2-pyrrolidinone (12.05 mg; 43%

yield) was obtained as a solid from 4-hydroxy-5-oxoproline (7.25 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 556.22.

Example 829

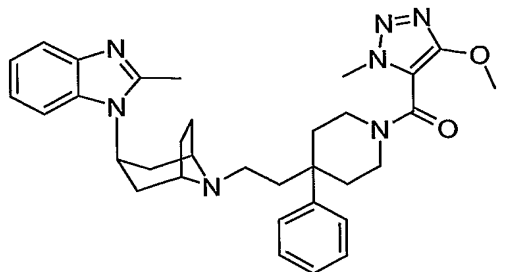
N,N-dimethyl-4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)carbonyl]-1,3-thiazol-2-amine



N,N-dimethyl-4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)carbonyl]-1,3-thiazol-2-amine (14.49 mg; 50% yield) was obtained as a solid from 2-(dimethylamino)-1,3-thiazole-4-carboxylic acid hydrobromide (12.65 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 583.23.

Example 830

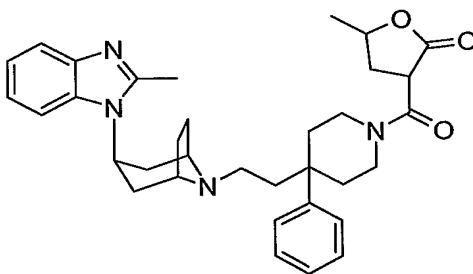
2-methyl-1-{8-[2-(1-{[1-methyl-4-(methyloxy)-1*H*-1,2,3-triazol-5-yl]carbonyl}-4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole



2-methyl-1-{8-[2-(1-{[1-methyl-4-(methoxy)-1*H*-1,2,3-triazol-5-yl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (2.99 mg; 11% yield) was obtained as a solid from 1-methyl-4-(methoxy)-1*H*-1,2,3-triazole-5-carboxylic acid (8.95 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 568.20.

Example 831

5-methyl-3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]dihydro-2(3*H*)-furanone



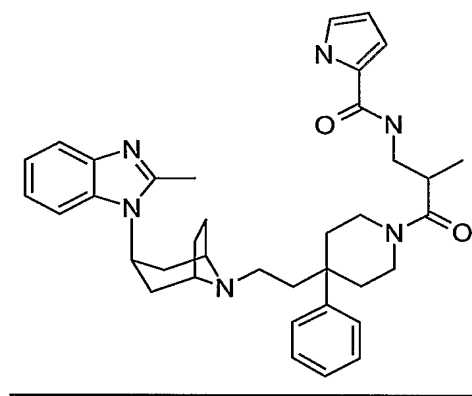
5-methyl-3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]dihydro-2(3*H*)-furanone (10.39 mg; 36% yield) was obtained as a solid from 5-methyl-2-oxotetrahydro-3-furancarboxylic acid (7.90 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride

570

(25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H): 569.25

Example 832

N-[2-methyl-3-(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxopropyl]-1H-pyrrole-2-carboxamide

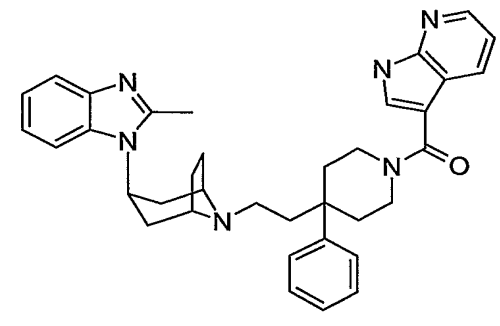


N-[2-methyl-3-(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-3-oxopropyl]-1H-pyrrole-2-carboxamide (13.35 mg; 44% yield) was obtained as a solid from 2-methyl-3-[(1H-pyrrol-2-ylcarbonyl)amino]propanoic acid (7.90 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H): 607.26

Example 833

2-methyl-1-(8-{2-[4-phenyl-1-(1H-pyrrolo[2,3-b]pyridin-3-ylcarbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole

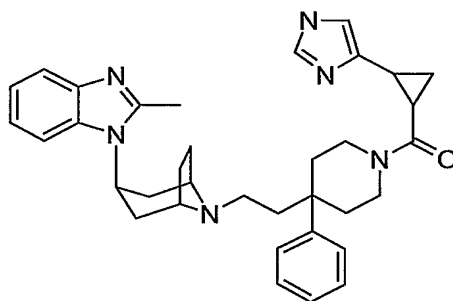
571



2-methyl-1-(8-{2-[4-phenyl-1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylcarbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-benzimidazole (9.29 mg; 32% yield) was obtained as a solid from 1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid (8.10 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 573.21

Example 834

1-{8-[2-(1-{[2-(1*H*-imidazol-4-yl)cyclopropyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1*H*-benzimidazole

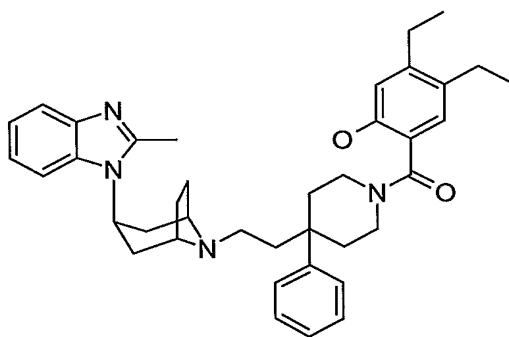


2-methyl-1-(8-{2-[4-phenyl-1-(1*H*-pyrrolo[2,3-*b*]pyridin-3-ylcarbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-benzimidazole (12.60 mg; 45% yield) was obtained as a solid from 2-(1*H*-imidazol-4-yl)cyclopropanecarboxylic acid hydrochloride (9.43 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-

benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H): 563.24

Example 835

4,5-diethyl-2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]phenol

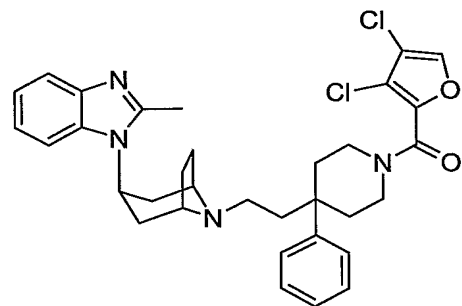


4,5-diethyl-2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]phenol (6.39 mg; 21% yield) was obtained as a solid from 4,5-diethyl-2-hydroxybenzoic acid (9.71 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H): 605.27.

Example 836

1-[8-(2-{1-[(3,4-dichloro-2-furanyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole

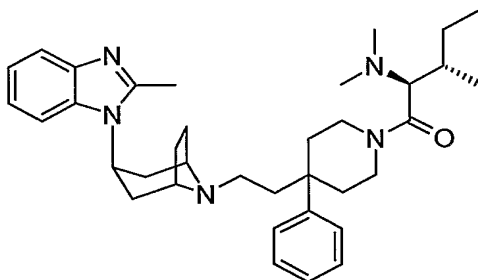
573



1-[8-(2-{1-[(3,4-dichloro-2-furanyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole (12.19 mg; 41% yield) was obtained as a solid from 3,4-dichloro-2-furancarboxylic acid (9.04 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 591.12.

Example 837

(2*S*,3*S*)-*N,N*,3-trimethyl-1-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-4-phenyl-1-piperidinyl)-1-oxo-2-pentanamine

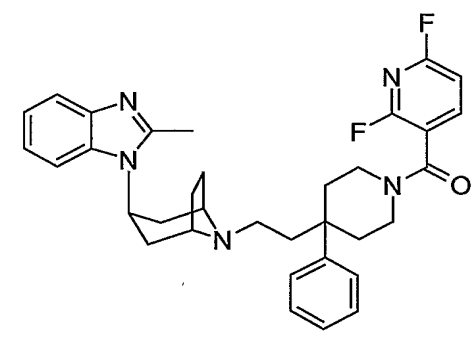


(2*S*,3*S*)-*N,N*,3-trimethyl-1-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)]-8-azabicyclo[3.2.1]oct-8-yl}ethyl)-4-phenyl-1-piperidinyl)-1-oxo-2-pentanamine (10.05 mg; 35% yield) was obtained as a solid from *N,N*-dimethyl-L-isoleucine (7.96 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride # (25 mg, 0.05

mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H): 570.15.

Example 838

1-[8-(2-{1-[(2,6-difluoro-3-pyridinyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

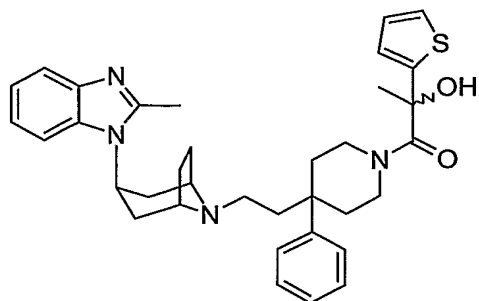


1-[8-(2-{1-[(2,6-difluoro-3-pyridinyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole (8.35 mg; 29% yield) was obtained as a solid from 2,6-difluoro-3-pyridinecarboxylic acid (7.95 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H): 570.19.

Example 839

1-(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)-1-oxo-2-(2-thienyl)-2-propanol

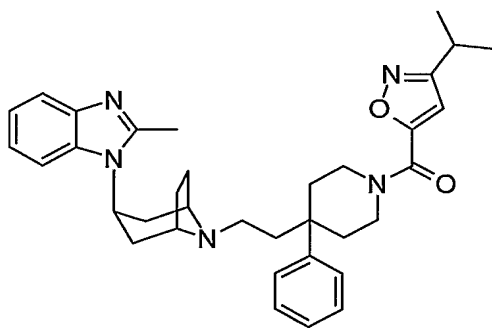
575



1-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)-1-oxo-2-(2-thienyl)-2-propanol (4.95 mg; 17% yield) was obtained as a solid from 2-hydroxy-2-(2-thienyl)propanoic acid (8.60mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 583.17.

Example 840

2-methyl-1-{8-[2-(1-{[3-(1-methylethyl)-5-isoxazolyl]carbonyl}-4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole

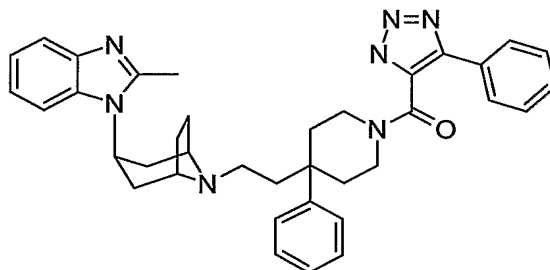


2-methyl-1-{8-[2-(1-{[3-(1-methylethyl)-5-isoxazolyl]carbonyl}-4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (11.29 mg; 40% yield) was obtained as a solid from 3-(1-methylethyl)-5-isoxazolecarboxylic acid hydrochloride (8.86mg, 0.05 mmol), 2-methyl-1-{8-[2-

(4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 566.27.

Example 841

2-methyl-1-[8-(2-{4-phenyl-1-[(4-phenyl-1*H*-1,2,3-triazol-5-yl)carbonyl]-4-piperidiny]ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole

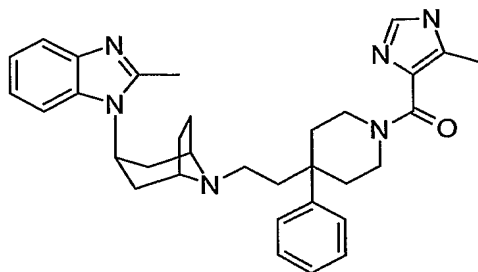


2-methyl-1-[8-(2-{4-phenyl-1-[(4-phenyl-1*H*-1,2,3-triazol-5-yl)carbonyl]-4-piperidiny]ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole (10.29 mg; 34% yield) was obtained as a solid from 4-phenyl-1*H*-1,2,3-triazole-5-carboxylic acid hydrochloride (9.45 mg, 0.05 mmol), 2-methyl-1-[8-[2-(4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 600.20.

Example 842

2-methyl-1-[8-(2-{1-[(4-methyl-1*H*-imidazol-5-yl)carbonyl]-4-phenyl-4-piperidiny]ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole

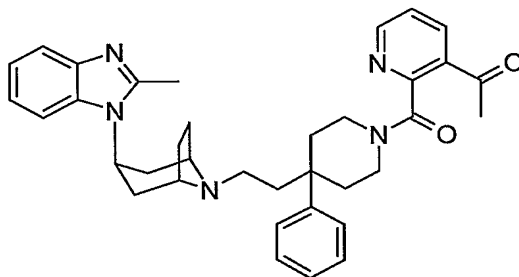
577



2-methyl-1-[8-(2-{1-[(4-methyl-1*H*-imidazol-5-yl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole (9.10 mg; 34% yield) was obtained as a solid from 4-methyl-1*H*-imidazole-5-carboxylic acid (6.30 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M-H): 535.52.

Example 843

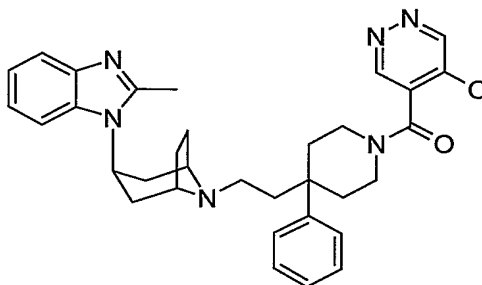
1-{2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinyl}ethanone



1-{2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinyl}ethanone (12.60 mg; 44% yield) was obtained as a solid from 3-acetyl-2-pyridinecarboxylic acid (9.35 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 576.24.

Example 844

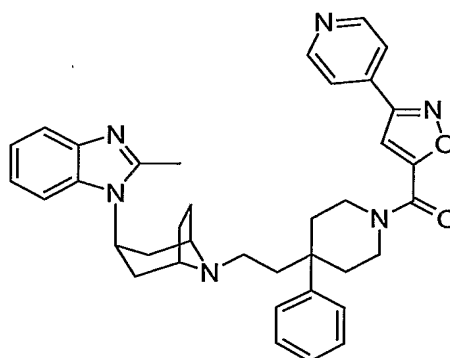
5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-4-pyridazinol



5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-4-pyridazinol (9.75mg; 35% yield) was obtained as a solid from 5-hydroxy-4-pyridazinecarboxylic acid (7.00 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 551.24.

Example 845

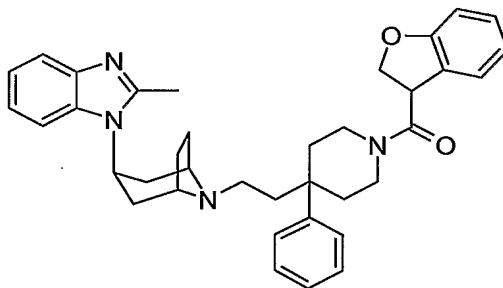
2-methyl-1-{8-[2-(4-phenyl-1-{3-(4-pyridinyl)-5-isoxazolyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole



2-methyl-1-{8-[2-(4-phenyl-1-{[3-(4-pyridinyl)-5-isoxazolyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (15.39mg; 51% yield) was obtained as a solid from 3-(4-pyridinyl)-5-isoxazolecarboxylic acid (9.51 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 601.16.

Example 846

1-(8-{2-[1-(2,3-dihydro-1-benzofuran-3-ylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole

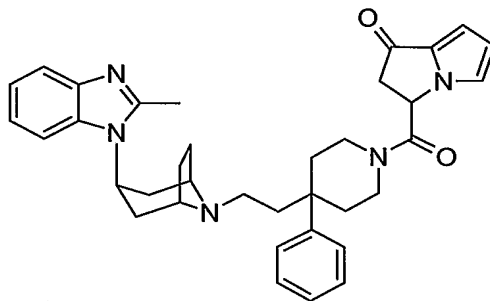


1-(8-{2-[1-(2,3-dihydro-1-benzofuran-3-ylcarbonyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (17.9 mg; 62% yield) was obtained as a solid from 2,3-dihydro-1-benzofuran-3-carboxylic acid (8.20 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 575.2.

Example 847

3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]pyrrol-1-one

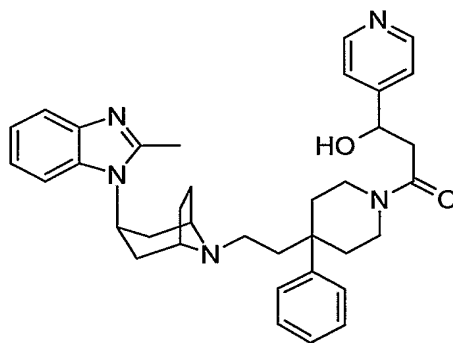
580



3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)carbonyl]-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]pyrrol-1-one (11.5 mg; 40% yield) was obtained as a solid from 1-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]pyrrole-3-carboxylic acid (9.35 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 576.22.

Example 848

3-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)-3-oxo-1-(4-pyridinyl)-1-propanol

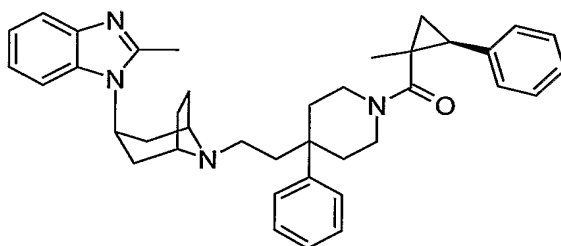


3-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)-3-oxo-1-(4-pyridinyl)-1-propanol (18.59mg; 64% yield) was obtained as a solid from 3-hydroxy-3-(4-pyridinyl)propanoic acid (8.35 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny)ethyl]-8-

azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 578.22.

Example 849

2-methyl-1-{8-[2-(1-[(2*S*)-1-methyl-2-phenylcyclopropyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole

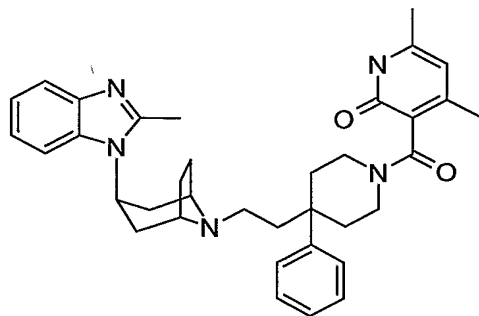


2-methyl-1-{8-[2-(1-[(2*S*)-1-methyl-2-phenylcyclopropyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (18.91 mg; 64% yield) was obtained as a solid from (2*S*)-1-methyl-2-phenylcyclopropanecarboxylic acid (8.81 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 587.26.

Example 850

4,6-dimethyl-3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2(1*H*)-pyridinone

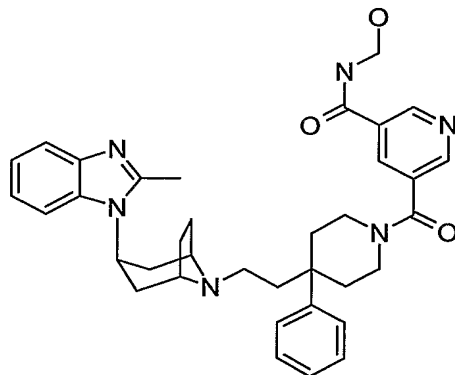
582



4,6-dimethyl-3-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2(1*H*)-pyridinone (17.84 mg; 62% yield) was obtained as a solid from 4,6-dimethyl-2-oxo-1,2-dihydro-3-pyridinecarboxylic acid (8.35 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 578.23.

Example 851

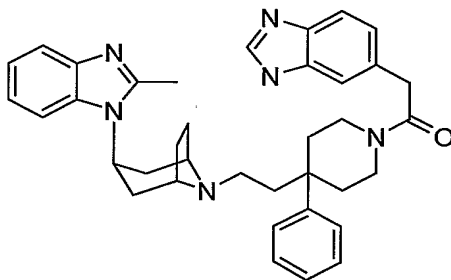
N-(hydroxymethyl)-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinecarboxamide



N-(hydroxymethyl)-5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-3-pyridinecarboxamide (5.55 mg; 18% yield) was obtained as a solid from 5-[[[(hydroxymethyl)amino]carbonyl]-3-pyridinecarboxylic acid (10.90 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 601.2.

Example 852

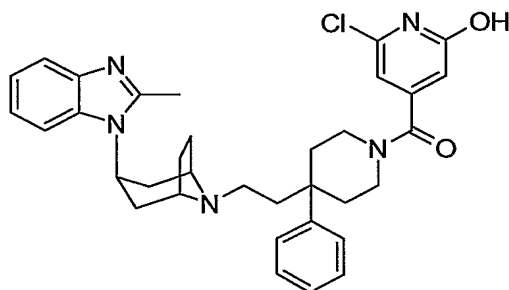
1-(8-{2-[1-(1*H*-benzimidazol-5-ylacetyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole



1-(8-{2-[1-(1*H*-benzimidazol-5-ylacetyl)-4-phenyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (15.20 mg; 52% yield) was obtained as a solid from 1*H*-benzimidazol-5-ylacetic acid (10.63 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 587.18.

Example 853

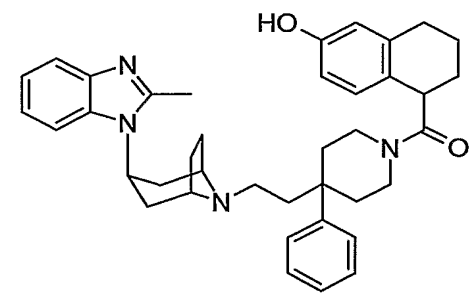
6-chloro-4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2(1*H*)-pyridinone



6-chloro-4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2(1*H*)-pyridinone (7.69 mg; 26% yield) was obtained as a solid from 6-chloro-2-oxo-1,2-dihydro-4-pyridinecarboxylic acid (8.67 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 584.16.

Example 854

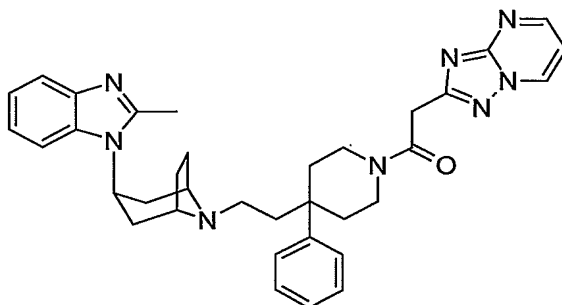
5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-5,6,7,8-tetrahydro-2-naphthalenol



5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)carbonyl]-5,6,7,8-tetrahydro-2-naphthalenol (18.15 mg; 60% yield) was obtained as a solid from 6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenecarboxylic acid (9.61 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 603.24.

Example 855

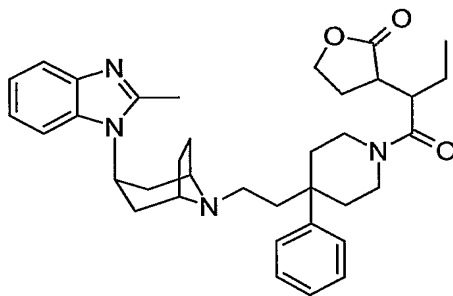
2-[2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)-2-oxoethyl][1,2,4]triazolo[1,5-*a*]pyrimidine



2-[2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)-2-oxoethyl][1,2,4]triazolo[1,5-*a*]pyrimidine (10.54 mg; 36% yield) was obtained as a solid from [1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylacetic acid (8.90 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 589.22.

Example 856

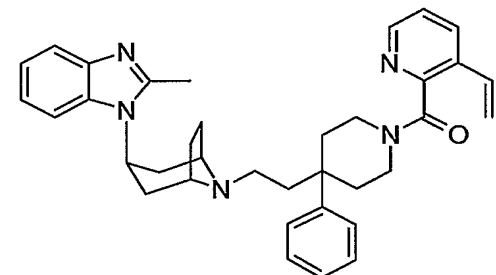
3-{1-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]propyl}dihydro-2(3*H*)-furanone



3-{1-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]propyl}dihydro-2(3*H*)-furanone (15.24 mg; 52% yield) was obtained as a solid from 2-(2-oxotetrahydro-3-furanyl)butanoic acid (8.60 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 583.26.

Example 857

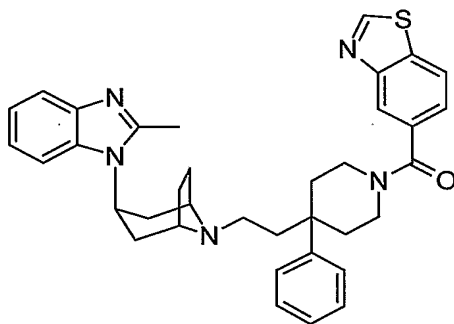
1-[8-(2-{1-[(3-ethenyl-2-pyridinyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole



1-[8-(2-{1-[(3-ethenyl-2-pyridinyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole (5.05 mg; 18% yield) was obtained as a solid from 3-ethenyl-2-pyridinecarboxylic acid (7.54 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 560.22.

Example 858

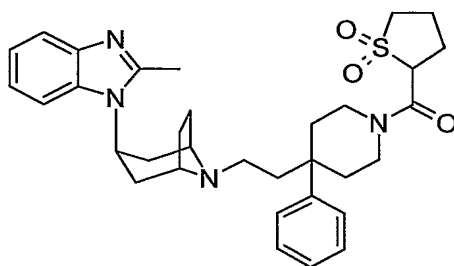
5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,3-benzothiazole



5-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,3-benzothiazole (7.95 mg; 27% yield) was obtained as a solid from 1,3-benzothiazole-5-carboxylic acid (8.95 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 590.17.

Example 859

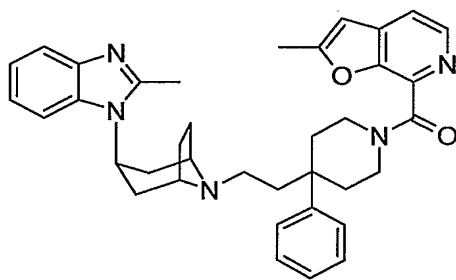
1-[8-(2-{1-[(1,1-dioxidotetrahydro-2-thienyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole



1-[8-(2-{1-[(1,1-dioxidotetrahydro-2-thienyl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole (8.89 mg; 31% yield) was obtained as a solid from tetrahydro-2-thiophenecarboxylic acid 1,1-dioxide (8.20 mg, 0.05 mmol), 2-methyl-1-[8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 575.16.

Example 860

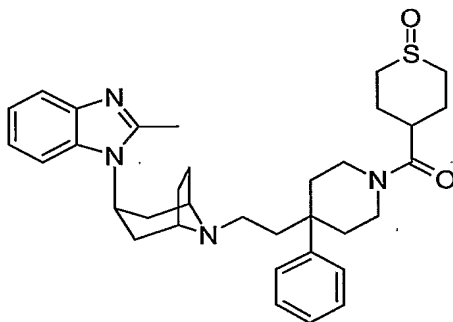
2-methyl-7-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]furo[2,3-*c*]pyridine



2-methyl-7-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]furo[2,3-*c*]pyridine (10.35 mg; 35% yield) was obtained as a solid from 2-methylfuro[2,3-*c*]pyridine-7-carboxylic acid (8.85 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 588.22.

Example 861

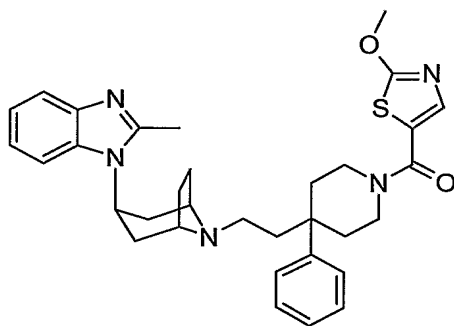
2-methyl-1-[8-(2-{1-[(1-oxidotetrahydro-2*H*-thiopyran-4-yl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole



2-methyl-1-[8-(2-{1-[(1-oxidotetrahydro-2*H*-thiopyran-4-yl)carbonyl]-4-phenyl-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole (15.85 mg; 55% yield) was obtained as a solid from tetrahydro-2*H*-thiopyran-4-carboxylic acid 1-oxide (8.11 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 573.24.

Example 862

2-methyl-1-{8-[2-(1-{[2-(methyloxy)-1,3-thiazol-5-yl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole

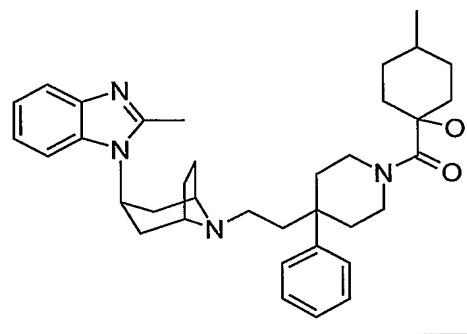


2-methyl-1-{8-[2-(1-{[2-(methyloxy)-1,3-thiazol-5-yl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole (10.75 mg; 38% yield) was obtained as a solid from 2-(methyloxy)-1,3-thiazole-5-carboxylic acid (7.95 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H): 570.21.

Example 863

4-methyl-1-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]cyclohexanol

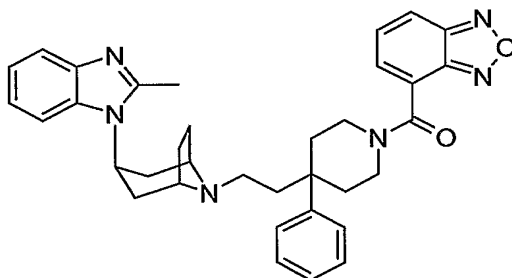
591



4-methyl-1-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]cyclohexanol (11.20 mg; 40% yield) was obtained as a solid from 1-hydroxy-4-methylcyclohexanecarboxylic acid (7.90 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (*M*+*H*): 569.27.

Example 864

4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2,1,3-benzoxadiazole

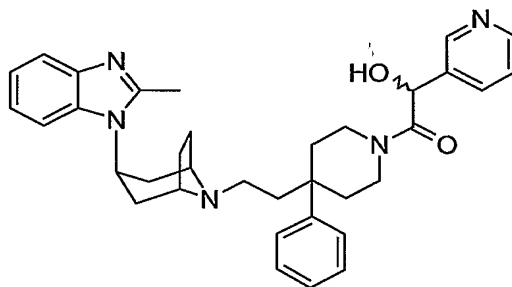


4-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2,1,3-benzoxadiazole (19.39 mg; 67% yield) was obtained as a solid from 2,1,3-benzoxadiazole-4-carboxylic acid (8.20 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05

mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H): 575.22.

Example 865

2-(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)-2-oxo-1-(3-pyridinyl)ethanol

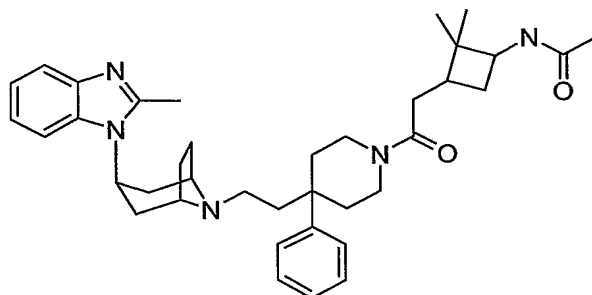


2-(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)-2-oxo-1-(3-pyridinyl)ethanol (15.04 mg; 54% yield) was obtained as a solid from hydroxy(3-pyridinyl)acetic acid (7.65 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H): 564.16.

Example 866

N-{2,2-dimethyl-3-[2-(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)-2-oxoethyl]cyclobutyl}acetamide

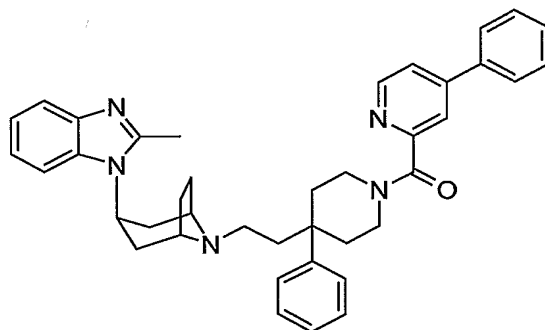
593



N-{2,2-dimethyl-3-[2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)]-2-oxoethyl]cyclobutyl}acetamide (15.85 mg; 52% yield) was obtained as a solid from [3-(acetlamino)-2,2-dimethylcyclobutyl]acetic acid (9.96 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny)]ethyl}-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (*M*+*H*): 610.30.

Example 867

2-methyl-1-[8-(2-{4-phenyl-1-[(4-phenyl-2-pyridinyl)carbonyl]-4-piperidiny]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-benzimidazole

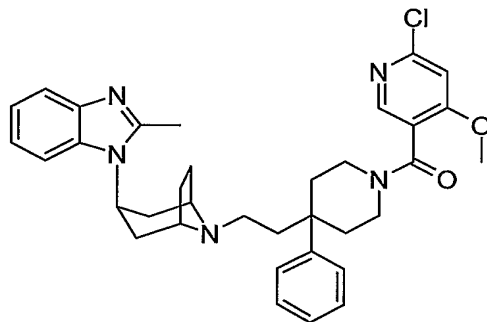


2-methyl-1-[8-(2-{4-phenyl-1-[(4-phenyl-2-pyridinyl)carbonyl]-4-piperidiny]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-benzimidazole (14.94 mg; 49% yield) was obtained as a solid from 4-phenyl-2-pyridinecarboxylic acid

(9.96 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 610.20.

Example 868

1-{8-[2-(1-{[6-chloro-4-(methyloxy)-3-pyridinyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1*H*-benzimidazole

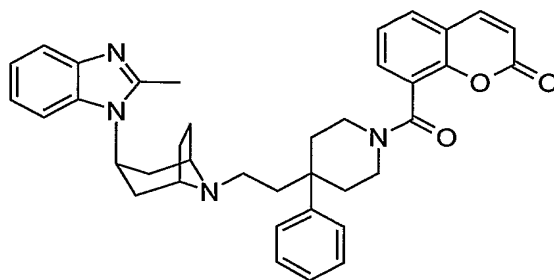


1-{8-[2-(1-{[6-chloro-4-(methyloxy)-3-pyridinyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1*H*-benzimidazole (17.05 mg; 57% yield) was obtained as a solid from 6-chloro-4-(methyloxy)-3-pyridinecarboxylic acid (9.37 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 598.19.

Example 869

8-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2*H*-chromen-2-one

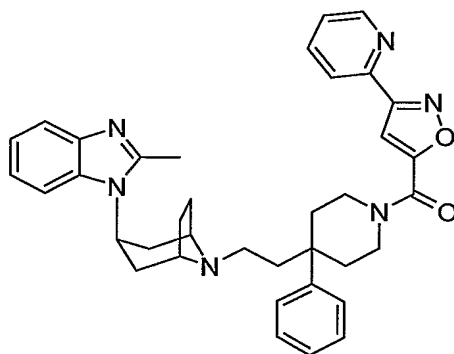
595



8-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-2*H*-chromen-2-one (20.64 mg; 68% yield) was obtained as a solid from 2-oxo-2*H*-chromene-8-carboxylic acid (9.50 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 601.19.

Example 870

2-methyl-1-{8-[2-(4-phenyl-1-{[3-(2-pyridinyl)-5-isoxazolyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole

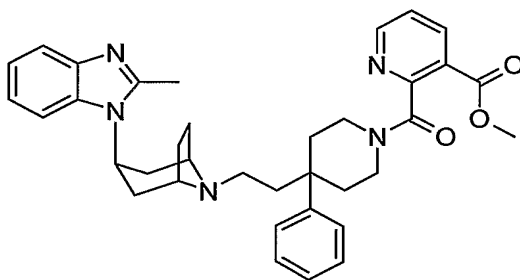


2-methyl-1-{8-[2-(4-phenyl-1-{[3-(2-pyridinyl)-5-isoxazolyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole (13.15 mg; 44% yield) was obtained as a solid from 3-(2-pyridinyl)-5-isoxazolecarboxylic acid (9.50 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-

azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 601.22.

Example 871

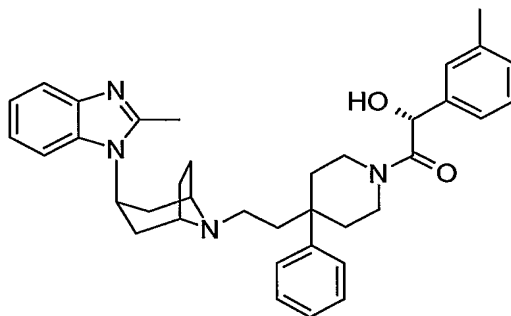
methyl 2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)carbonyl]-3-pyridinecarboxylate



Methyl 2-[(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)carbonyl]-3-pyridinecarboxylate (8.45 mg; 28% yield) was obtained as a solid from 3-[(methoxy)carbonyl]-2-pyridinecarboxylic acid (9.05 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 592.21.

Example 872

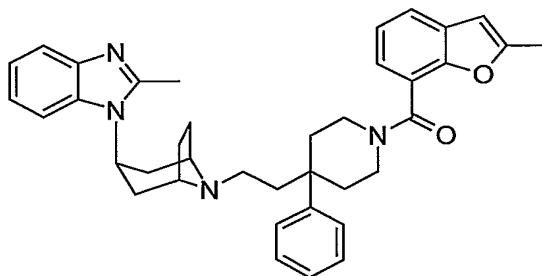
(1*R*)-2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)-1-(3-methylphenyl)-2-oxoethanol



(1*R*)-2-(4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidiny)-1-(3-methylphenyl)-2-oxoethanol (11.85 mg; 41% yield) was obtained as a solid from (2*R*)-hydroxy(3-methylphenyl)ethanoic acid (8.30 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* (M+H): 577.24.

Example 873

2-methyl-1-[8-(2-{1-[(2-methyl-1-benzofuran-7-yl)carbonyl]-4-phenyl-4-piperidiny}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole

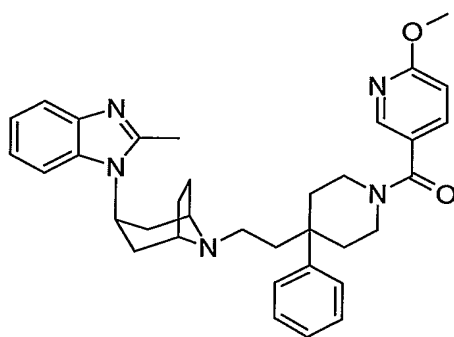


2-methyl-1-[8-(2-{1-[(2-methyl-1-benzofuran-7-yl)carbonyl]-4-phenyl-4-piperidiny}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1*H*-benzimidazole (12.30 mg; 42% yield) was obtained as a solid from 2-methyl-1-benzofuran-7-carboxylic acid (8.80 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidiny)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole hydrochloride (25 mg, 0.05

mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H):587.22.

Example 874

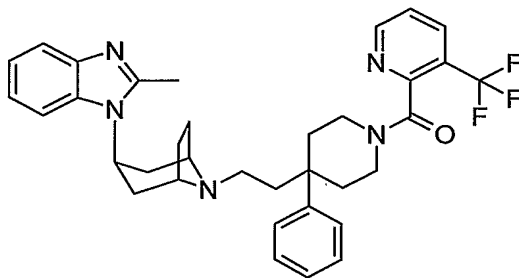
2-methyl-1-{8-[2-(1-{[6-(methyloxy)-3-pyridinyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole



2-methyl-1-{8-[2-(1-{[6-(methyloxy)-3-pyridinyl]carbonyl}-4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole (13.0 mg; 43% yield) was obtained as a solid from 6-(methyloxy)-3-pyridinecarboxylic acid (9.37 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H):598.18.

Example 875

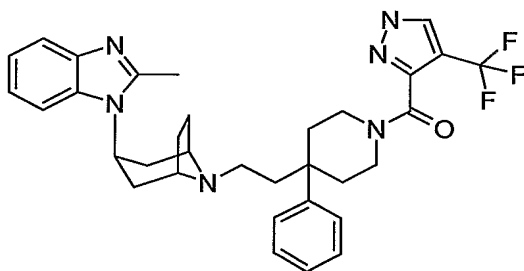
2-methyl-1-{8-[2-(4-phenyl-1-{[3-(trifluoromethyl)-2-pyridinyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole



2-methyl-1-{8-[2-(4-phenyl-1-{[3-(trifluoromethyl)-2-pyridinyl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole (11.89 mg; 39% yield) was obtained as a solid from 3-(trifluoromethyl)-2-pyridinecarboxylic acid (9.56 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole hydrochloride (25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H):602.19.

Example 876

2-methyl-1-{8-[2-(4-phenyl-1-{[4-(trifluoromethyl)-1H-pyrazol-3-yl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole



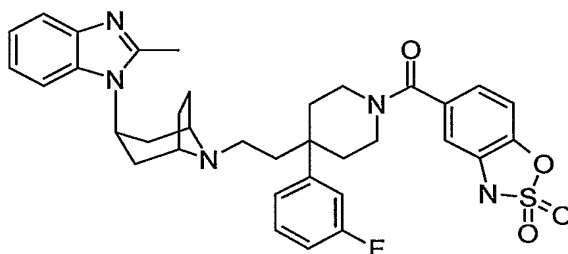
2-methyl-1-{8-[2-(4-phenyl-1-{[4-(trifluoromethyl)-1H-pyrazol-3-yl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole (3.94 mg; 13% yield) was obtained as a solid from 4-(trifluoromethyl)-1H-pyrazole-3-carboxylic acid (9.00 mg, 0.05 mmol), 2-methyl-1-{8-[2-(4-phenyl-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole hydrochloride

600

(25 mg, 0.05 mmol) and HATU (19 mg, 0.05 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H):591.19.

Example 877

5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]-3H-1,2,3-benzoxathiazole 2,2-dioxide



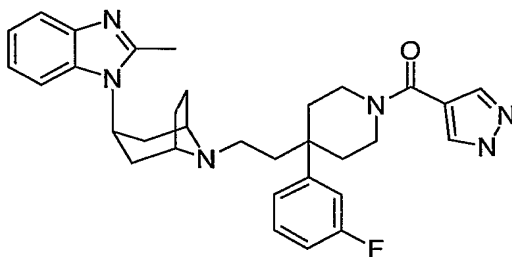
5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]-3H-1,2,3-benzoxathiazole 2,2-dioxide

(18 mg; 27% yield) was obtained as a solid from 3H-1,2,3-benzoxathiazole-5-carboxylic acid 2,2-dioxide (22 mg, 0.1 mmol), 1-(8-{2-[4-(3-fluorophenyl)-4-piperidiny]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole hydrochloride (50 mg, 0.1 mmol) and HATU (38 mg, 0.1 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H): 644.29.

Example 878

1-(8-{2-[4-(3-fluorophenyl)-1-(1H-pyrazol-4-yl)carbonyl]-4-piperidiny]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

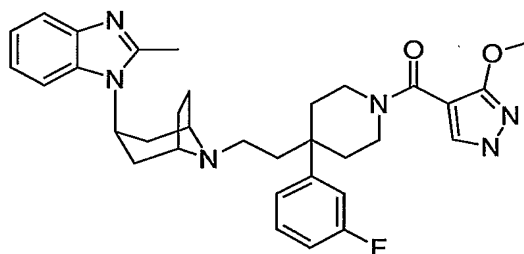
601



1-(8-{2-[4-(3-fluorophenyl)-1-(1H-pyrazol-4-ylcarbonyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (38 mg; 37% yield) was obtained as a solid from 1H-pyrazole-4-carboxylic acid (21 mg, 0.2 mmol), 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole hydrochloride (100 mg, 0.2 mmol) and HATU (73 mg, 0.2 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H): 541.20.

Example 879

1-{8-[2-(4-(3-fluorophenyl)-1-{[3-(methyloxy)-1H-pyrazol-4-yl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole

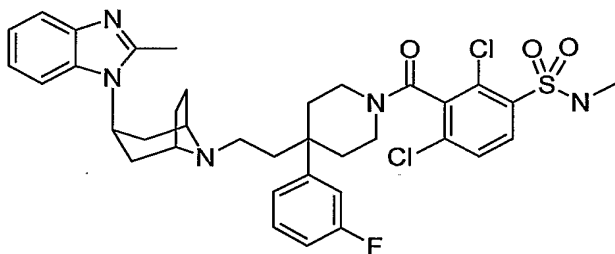


1-{8-[2-(4-(3-fluorophenyl)-1-{[3-(methyloxy)-1-(phenylmethyl)-1H-pyrazol-4-yl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1H-benzimidazole was obtained as a crude mixture from 3-(methyloxy)-1-(phenylmethyl)-1H-pyrazole-4-carboxylic acid (23 mg, 0.1 mmol), 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole hydrochloride (50 mg, 0.1 mmol) and HATU (38 mg, 0.1 mmol) following the procedure outlined in example 5. ES-LCMS m/z (M+H): 661.46.

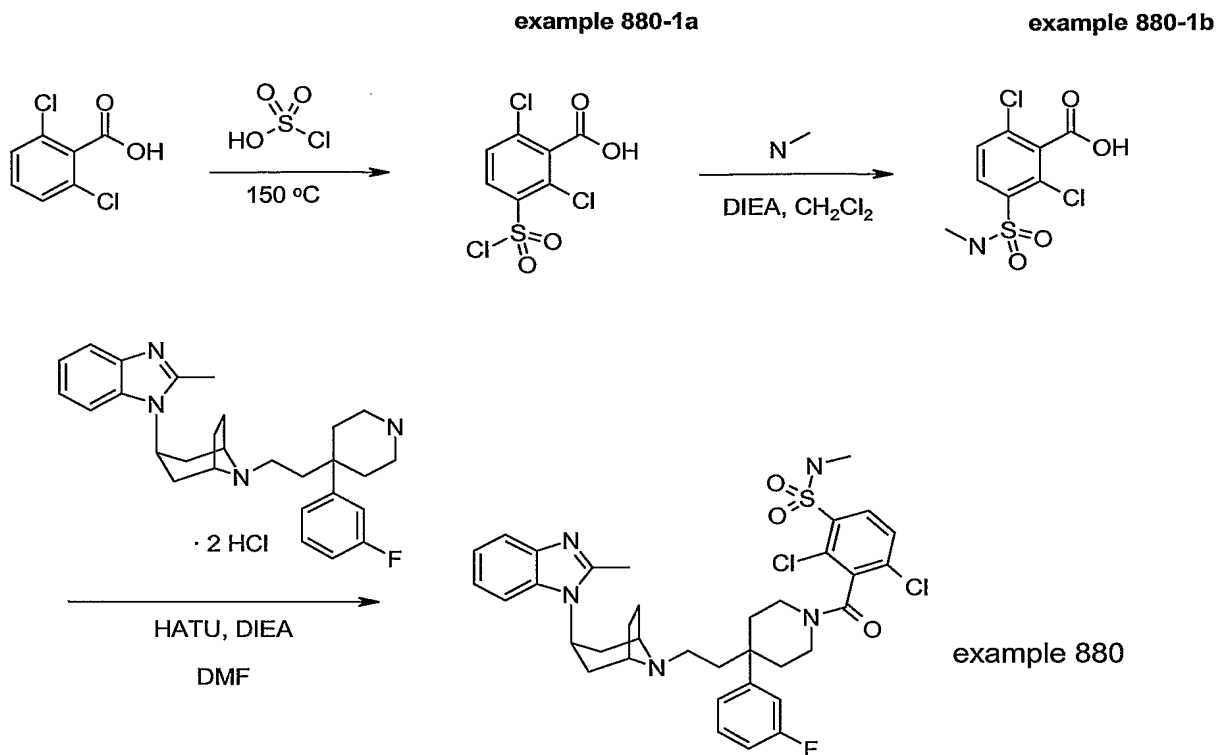
The crude mixture was then treated with PdCl_2 (25 mg) under 50 psi H_2 to provide 1-{8-[2-(4-(3-fluorophenyl)-1-{[3-(methoxy)-1*H*-pyrazol-4-yl]carbonyl}-4-piperidinyl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1*H*-benzimidazole as solid (30, 52%). ES-LCMS m/z (M+H): 571.24

Example 880

2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-*N*-methylbenzenesulfonamide



Example 880 was prepared according to figure below.



Synthesis of 880-1a
2,6-dichloro-3-(chlorosulfonyl)benzoic acid

Chlorosulfonic acid was slowly added to 2,6-dichlorobenzoic acid at RT under N₂. The reaction was heated to 150 °C for 3 h, then slowly poured over ice and the product extracted into Et₂O. The organic layer was dried over MgSO₄, filtered and concentrated to give 2,6-dichloro-3-(chlorosulfonyl)benzoic acid 880-1a as a brown solid (12.9 g, 85% yield).

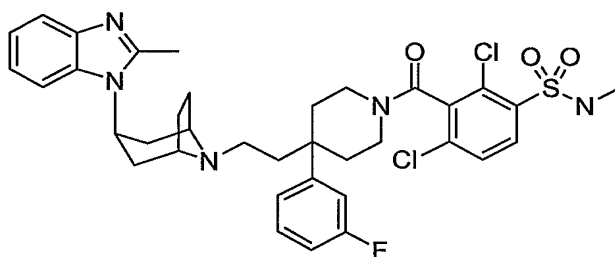
¹H NMR (400 MHz, DMSO) δ 13.42 (broad s, 1H), 7.88 (d, *J* = 8. Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H).

Synthesis of 880-1b
2,6-dichloro-3-[(methylamino)sulfonyl]benzoic acid

A mixture of 2,6-dichloro-3-(chlorosulfonyl)benzoic acid 880-1a (200 mg, 0.69 mmol, 1 equiv) and 4 mL CH₂Cl₂ was treated with diisopropylamine (248 μ L, 1.38 mmol, 2 equiv) and 2M methyl amine (415 μ L, 0.83 mmol, 1.2 equiv). The reaction was stirred at RT overnight, wherein the crude mixture contained 2,6-dichloro-3-[(methylamino)sulfonyl]benzoic acid 880-1b. The mixture was carried directly into the following reaction. ES-LCMS m/z 284.0 (M-H)

Synthesis of 880

2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide



To a solution of 1-(8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (100 mg, 0.16 mmol, 1 equiv) and *N,N*-diisopropylethyl amine (117 μ L, 0.66 mmol, 4 equiv) in dimethylformamide (2 mL) was added the mixture of 2,6-dichloro-3-[(methylamino)sulfonyl]benzoic acid 880-1b. After stirring at RT for several min, *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluroniumhexafluorophosphate (62 mg, 0.16 mmol, 1 equiv) was added and the reaction was stirred for 18 h. The mixture was partitioned between dichloromethane and satd. aq. NaHCO₃. The organic layer was dried and concentrated and the residue was purified by SiO₂ flash column chromatography (100% EtOAc \rightarrow 10% 2M NH₃ in MeOH in EtOAc) to provide 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-

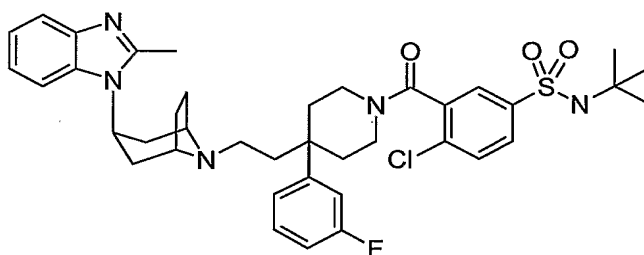
605

methylbenzenesulfonamide (example 880) as a white solid (25 mg, 22% yield).

^1H NMR (300 MHz, CDCl_3) δ 8.05 (m, 1H), 7.65 (m, 1H), 7.49 (m, 1H), 7.39-7.29 (m, 3H), 7.19-6.95 (m, 5H), 5.34 (m, 1H), 4.60 (m, 1H), 4.27 (m, 1H), 3.48-3.12 (m, 6H), 2.66 (m, 3H), 2.56 (m, 3H), 2.42-2.27 (m, 3H), 2.22-1.76 (m, 7H), 1.64 (m, 2H), 1.42 (m, 2H). ES-LCMS m/z 712.2 (M+H).

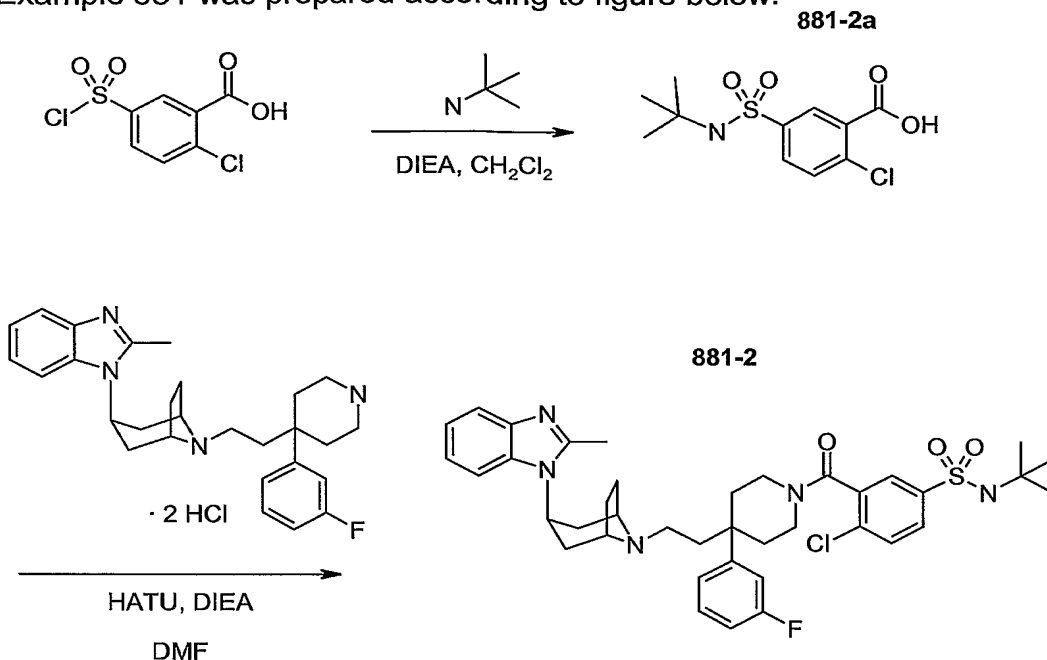
Example 881

4-chloro-N-(1,1-dimethylethyl)-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny)carbonyl]benzenesulfonamide



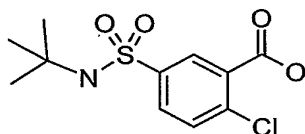
606

Example 881 was prepared according to figure below.



Synthesis of 881-2a

2-chloro-5-[[[(1,1-dimethylethyl)amino]sulfonyl]benzoic acid



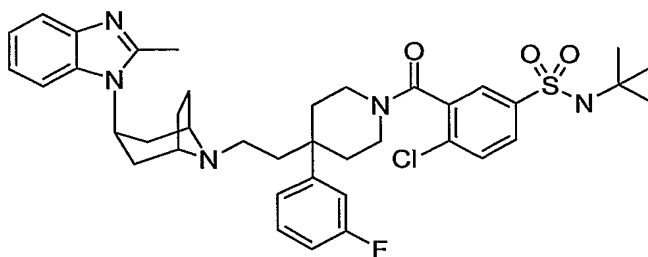
Prepared from a mixture of 2-chloro-5-(chlorosulfonyl)benzoic acid (200 mg, 0.78 mmol, 1 equiv) *tert*-butyl amine (98 μ L, 0.94 mmol, 1.2 equiv) and DIEA (248 μ L, 1.38 mmol, 2 equiv) following the general procedure for 2,6-dichloro-3-[(methylamino)sulfonyl]benzoic acid 881-1b. The crude reaction mixture was carried on without further purification.

ES-LCMS m/z 315.2 ($M+Na$)

Synthesis of 881

4-chloro-N-(1,1-dimethylethyl)-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny)carbonyl]benzenesulfonamide

607



Prepared from a mixture of 2-chloro-5-[[[(1,1-dimethylethyl)amino]sulfonyl]benzoic acid

2b, 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (100 mg, 0.16 mmol, 1 equiv), DIEA (117 μ L, 0.66 mmol, 4 equiv) and HATU (62 mg, 0.16 mmol, 1 equiv) following the general procedure for 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide

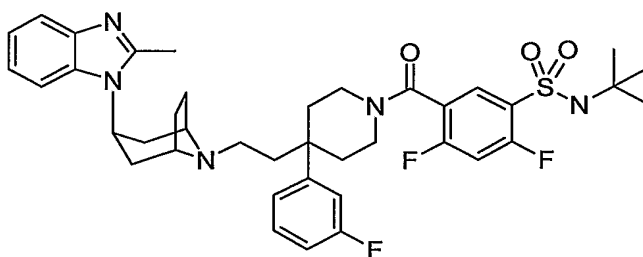
example 880. The crude product was purified by column chromatography on silica gel eluting with 10% 2M NH_3 in methanol in ethyl acetate to afford 4-chloro-N-(1,1-dimethylethyl)-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide as a white solid (40.3 mg, 35% yield).

^1H NMR (300 MHz, CDCl_3) δ 7.89-7.80 (m, 1H), 7.71-7.64 (m, 1H), 7.55-7.48 (m, 1H), 7.38-7.26 (m, 3H), 7.19-6.94 (m, 6H), 4.92-4.54 (m, 2H), 4.23 (m, 1H), 3.47-3.04 (m, 6H), 2.56 (m, 3H), 2.54-1.34 (m, 14H), 1.24 (m, 9H). ES-LCMS m/z 720.2 ($\text{M}+\text{H}$).

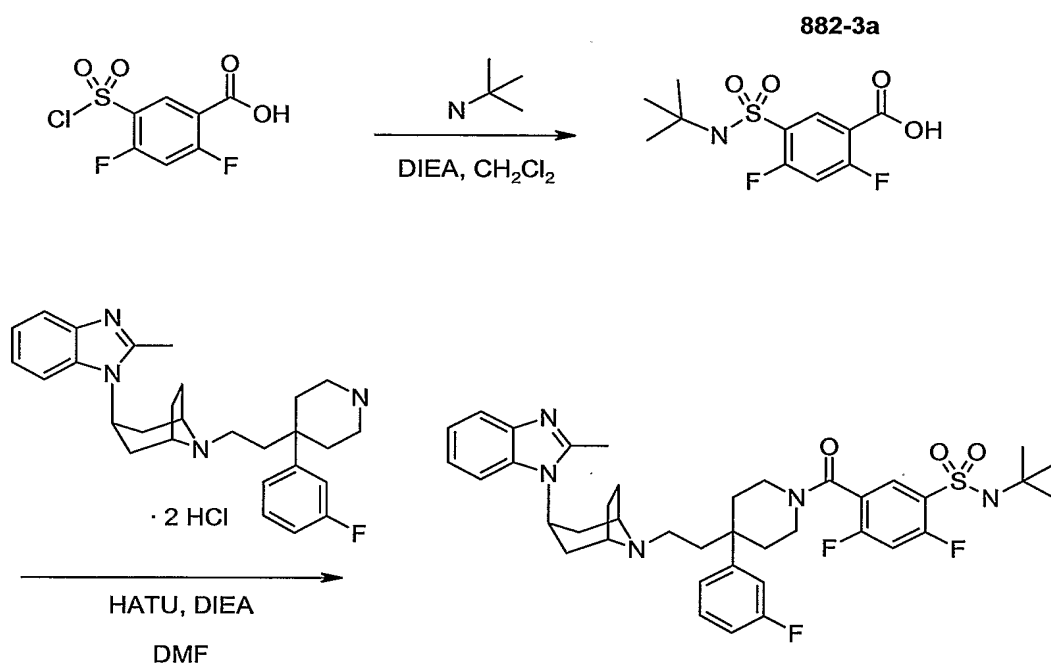
Example 882

N-(1,1-dimethylethyl)-2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide

608

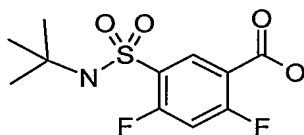


Prepared according to figure below.



Synthesis of 882-3a

5-[(1,1-dimethylethyl)amino]sulfonyl-2,4-difluorobenzoic acid



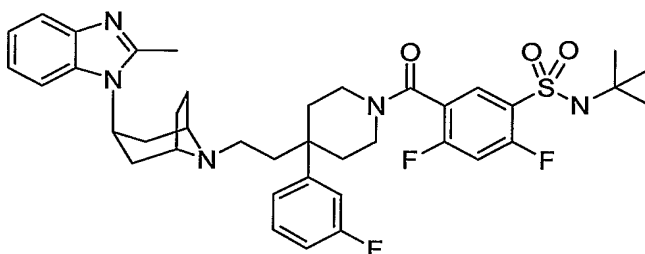
Prepared from a mixture of 5-(chlorosulfonyl)-2,4-difluorobenzoic acid (200 mg, 0.78 mmol, 1 equiv), *tert*-butyl amine (98 μ L, 0.94 mmol, 1.2 equiv) and DIEA (280 μ L, 1.56 mmol, 2 equiv) following the general procedure for 2,6-

dichloro-3-[(methylamino)sulfonyl]benzoic acid 880-1b. The crude reaction mixture was carried on without further purification.

ES-LCMS m/z 292.3 (M-H)

Synthesis of 882

N-(1,1-dimethylethyl)-2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide



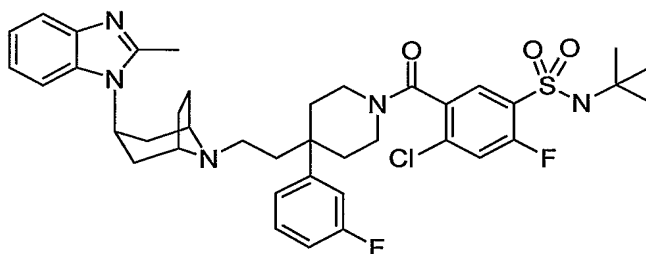
Prepared from a mixture of 5-[(1,1-dimethylethyl)amino]sulfonyl}-2,4-difluorobenzoic acid 882-3b 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (100mg, 0.16 mmol, 1 equiv), DIEA (117 μ L, 0.66 mmol, 4 equiv) and HATU (62 mg, 0.16 mmol, 1 equiv) following the general procedure for 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide 1. The crude product was purified by column chromatography on silica gel eluting with 10% 2M NH_3 in methanol in ethyl acetate to afford N-(1,1-dimethylethyl)-2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide (example 882) as a white solid (46 mg, 40% yield).

^1H NMR (400 MHz, CDCl_3) δ 8.00 (m, 1H), 7.66 (m, 1H), 7.93-6.95 (m, 9H), 4.86 (m, 1H), 4.62 (m, 1H), 4.15 (m, 2H), 3.44-3.14 (m, 5H), 2.92 (m, 3H),

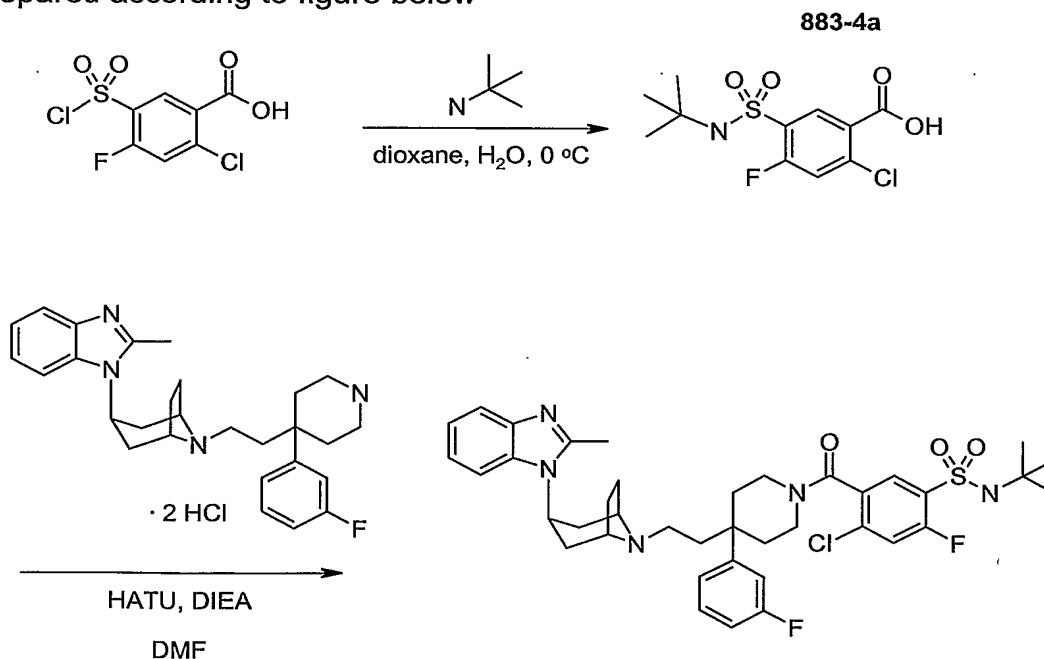
2.58-1.60 (m, 14H), 1.25 (m, 9H). HRMS m/z (M+H): Calcd for $C_{39}H_{46}F_3N_5O_3S$, 722.34; found 722.3352.

Example 883

4-chloro-N-(1,1-dimethylethyl)-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny)carbonyl]benzenesulfonamide



Prepared according to figure below



Synthesis of 883-4a

2-chloro-5-[(1,1-dimethylethyl)amino]sulfonyl-4-fluorobenzoic acid

611

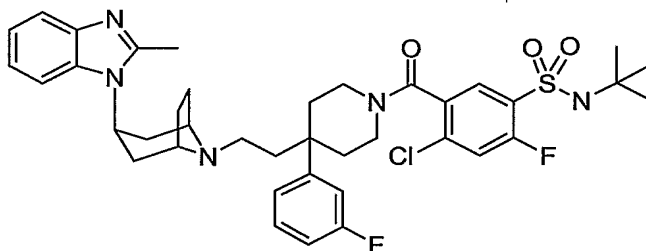


tert-Butyl amine (77 mL, 0.7 mol, 10 equiv) was added to 300 mL dioxane at 0 °C. Ice chips were added to the flask for several minutes before the addition of 2-chloro-5-(chlorosulfonyl)-4-fluorobenzoic acid (20 g, 73.24 mmol, 1 equiv). Both the internal and external temperature of the reaction was maintained at or below 0 °C for 2 h. The reaction was then concentrated half-way and acidified to pH 2 with 1N HCl. The product was extracted into EtOAc. The organics were dried over Na₂SO₄, filtered and concentrated down to give 2-chloro-5-[[(1,1-dimethylethyl)amino]sulfonyl]-4-fluorobenzoic acid 883-4a as a brown solid (21 g; 92% yield).

¹H NMR (400 MHz, DMSO) δ 8.23 (d, *J* = 7.8 Hz, 1H), 8.06 (broad s, 1H), 7.82 (d, *J* = 9.8 Hz, 1H). ES-LCMS *m/z* 308.2 (M-H)

Synthesis of 883

4-chloro-N-(1,1-dimethylethyl)-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]benzenesulfonamide



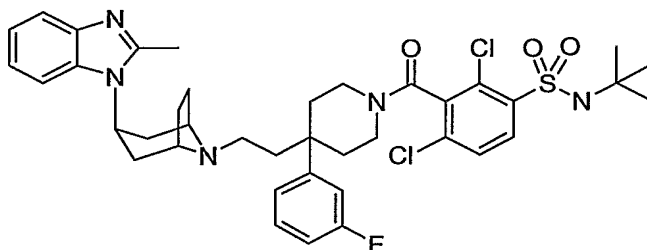
To a solution of 1-(8-{2-[4-(3-fluorophenyl)-4-piperidiny]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (32.0 g, 61.6 mmol, 1 equiv) in dimethylformamide (300 mL) was added 2-chloro-5-[[(1,1-dimethylethyl)amino]sulfonyl]-4-fluorobenzoic acid 883-4b (21 g, 67.8 mmol, 1.1 equiv) and *N,N*-diisopropylethyl amine (44 mL, 0.25 mol, 4 equiv). After

stirring at RT for several min, *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluroniumhexafluorophosphate (23.4 g, 61.6 mmol, 1 equiv) was added and the reaction was stirred for 2 h. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with satd. aq. NaHCO₃, H₂O and satd. aq. NaCl, then dried over Na₂SO₄, filtered and concentrated. The residue was taken up in 200 mL MeOH and stirred with Amberjet 4400 OH Basic Ion Exchanger (60 g) for 1 h. The mixture was filtered and concentrated and the residue was purified by silica gel flash column chromatography in 20% 2M NH₃ in MeOH in EtOAc to afford 4-chloro-*N*-(1,1-dimethylethyl)-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]benzenesulfonamide (example 883) as a white solid (21g; 46% yield).

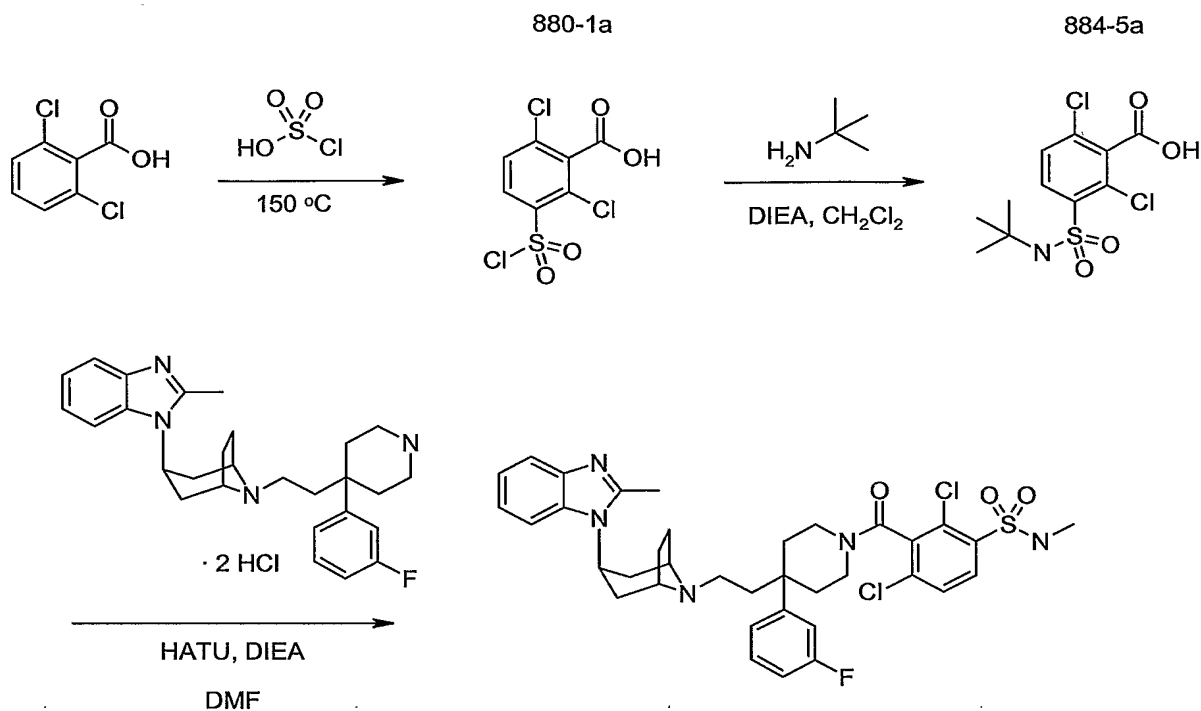
¹H NMR (400 MHz, CDCl₃) δ 8.00 (m, 1H), 7.86–7.76 (m, 2H), 7.49 (m, 1H), 7.44–7.35 (m, 2H), 7.23 (m, 2H), 7.15–7.04 (m, 3H), 4.55–4.45 (m, 1H), 3.98–3.86 (m, 1H), 3.42–3.35 (m, 1H), 3.25 (m, 2H), 3.05–2.96 (m, 1H), 2.45 (m, 3H), 2.39–2.32 (m, 2H), 2.23–1.99 (m, 2H), 1.92–1.72 (m, 11H), 1.60 (m, 2H), 1.12 (m, 9H). HRMS *m/z* (M+H) Calcd for C₃₉H₄₆ClF₂N₅O₃S, 738.30; Found, 738.30.

Example 884

2,4-dichloro-*N*-(1,1-dimethylethyl)-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]benzenesulfonamide

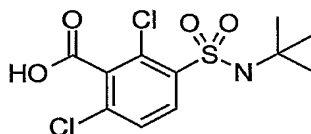


Example 884 was prepared according to figure below.



Synthesis of 884-5a

2,6-dichloro-3-[(1,1-dimethylethyl)amino]sulfonyl}benzoic acid

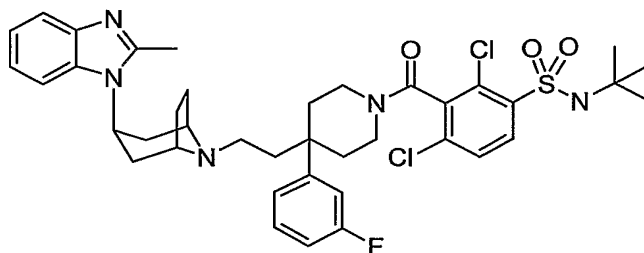


Prepared from a mixture of 2,6-dichloro-3-[(1,1-dimethylethyl)amino]sulfonyl}benzoic acid 884-5a (200mg, 0.69 mmol, 1 equiv), *tert*-butyl amine and DIEA (248 μ L, 1.38 mmol, equiv) following the general procedure for 2,6-dichloro-3-[(methylamino)sulfonyl]benzoic acid 880-1b. The crude reaction mixture was carried on without further purification.

ES-LCMS m/z 327.4 (M+H)

Synthesis of 884

2,4-dichloro-N-(1,1-dimethylethyl)-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide

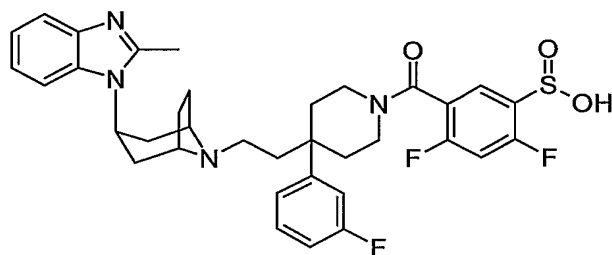


Prepared from a mixture of 2,6-dichloro-3-[(1,1-dimethylethyl)amino]sulfonylbenzoic acid 884-5a, 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (100 mg, 0.16 mmol, 1 equiv), DIEA (117 μ L, 0.66 mmol, 4 equiv) and HATU (62 mg, 0.16 mmol, 1 equiv) following the general procedure for 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide (example 880). The crude product was purified by column chromatography on silica gel eluting with 10% 2M NH_3 in methanol in ethyl acetate to afford 2,4-dichloro-N-(1,1-dimethylethyl)-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide 5 as a white solid (21 mg, 17% yield).

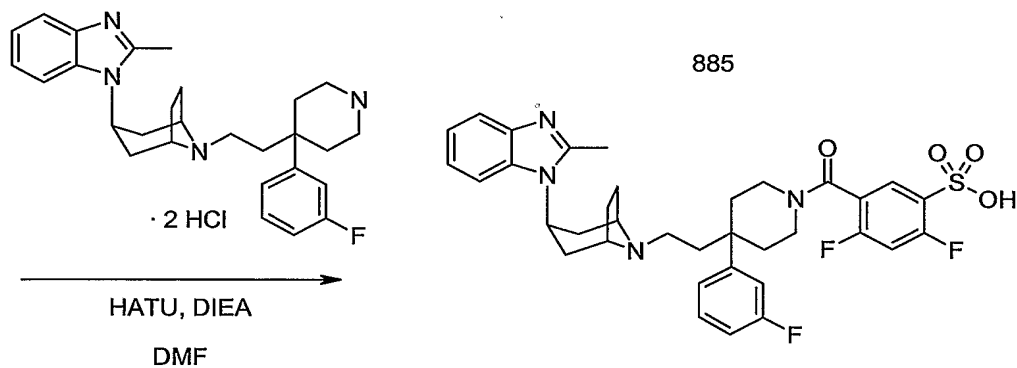
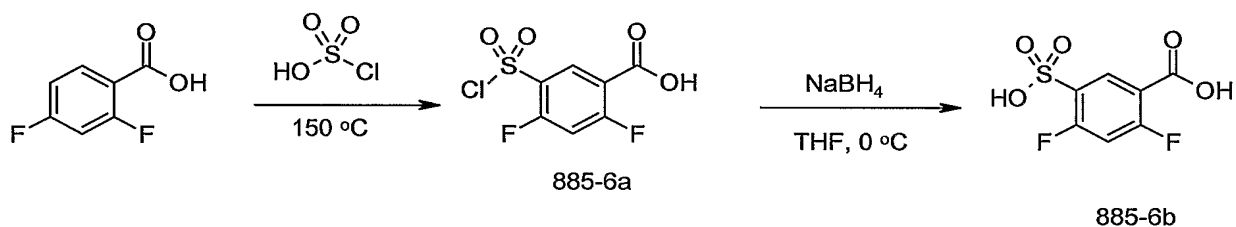
^1H NMR (400 MHz, CDCl_3) δ 8.08 (m, 1H), 7.66 (m, 1H), 7.47 (m, 1H), 7.39-7.26 (m, 3H), 7.20-6.95 (m, 5H), 4.98 (m, 1H), 4.61 (m, 1H), 4.27 (m, 1H), 3.71 (m, 1H), 3.51 – 3.07 (m, 7H), 2.57 (m, 3H), 2.47-1.37 (m, 11H), 1.23 (m, 9H). HRMS m/z (M+H) Calcd for $\text{C}_{39}\text{H}_{46}\text{Cl}_2\text{FN}_5\text{O}_3\text{S}$, 754.2761: Found, 754.2761.

Example 885

2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny)carbonyl]benzenesulfinic acid

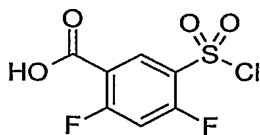


Example was prepared according the figure below.



Synthesis of 885-6a

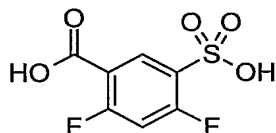
5-(chlorosulfonyl)-2,4-difluorobenzoic acid



A mixture of chlorosulfonic acid (200 mL) and 2,4-difluorobenzoic acid (40 g, 253 mmol, 1 equiv) was heated to 155 °C for 3 h. The reaction was cooled to RT and poured slowly over ice. The product was extracted into ether and the organics dried over MgSO₄, filtered and concentrated to give 5-(chlorosulfonyl)-2,4-difluorobenzoic acid **6a** as brown solid (61 g, 94% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.98 (broad s, 1H), 8.72 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 9.5 Hz, 1H). ES-LCMS *m/z* 255.3 (M-H)

Synthesis of 885-6b
2,4-difluoro-5-sulfobenzoic acid

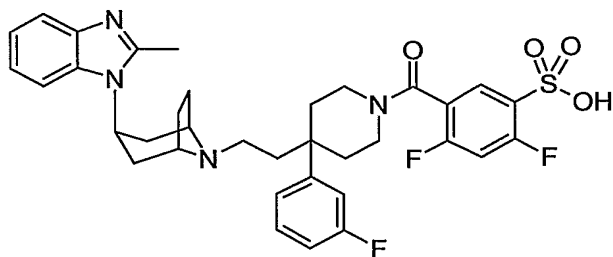


Sodium borohydride (0.59 g, 15.6 mmol, 8 equiv) was added portionwise to a solution of 5-(chlorosulfonyl)-2,4-difluorobenzoic acid **885-6a** (0.5 g, 1.9 mmol, 1 equiv) in 10 mL THF at 0 °C. The reaction was stirred at this temperature for 1 h and then concentrated down and the residue acidified to pH 2 with 5N HCl. The precipitate was removed by filtration and the liquid concentrated down to provide 2,4-difluoro-5-sulfobenzoic acid **885-6b** as a white solid (433 mg, 100% yield)

¹H NMR (400 MHz, DMSO) δ 8.18 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 10.2 Hz, 1H).

Synthesis of example 885
2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]benzenesulfonic acid

617



Prepared from a mixture of 2,4-difluoro-5-sulfobenzoic acid 885-6b(580 mg, 0.58 mmol, 2 equiv), 1-(8-{2-[4-(3-fluorophenyl)-4-piperidiny]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (150 mg, 0.29 mmol, 1 equiv), DIEA (260 μ L, 1.45 mmol, 5 equiv) and HATU (110 mg, 0.29 mmol, 1 equiv) following the general procedure for 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny)carbonyl]-N-methylbenzenesulfonamid, example 880. The crude product was purified by prep HPLC (HPLC Method C) to afford 2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny)carbonyl]benzenesulfonic acid (example 885) as a white solid (40 mg, 22% yield).

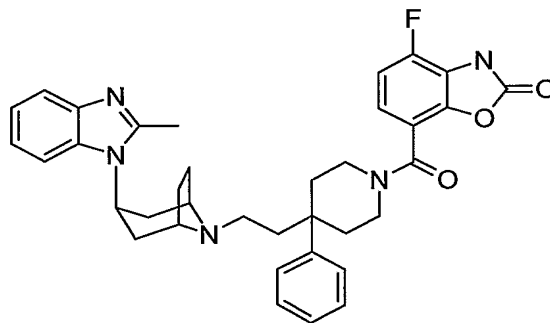
^1H NMR (400 MHz, CDCl_3) δ 7.64 (m, 1H), 7.53 (m, 1H), 7.47-7.40 (m, 2H), 7.27-7.03 (m, 6H), 4.88 (m, 1H), 3.88-3.05 (m, 4H), 2.64-2.34 (m, 14H, 2.22-1.80 (m, 8H). ES-LCMS m/z 651.3 (M^+H).

HPLC Method C

Preparative High Pressure Liquid Chromatography data was acquired using a Waters LC-UV system. The system operates using a Waters Symmetry Shield RP18 3.9x150mm, 5 μ m column at 35mL/minute. The mobile phase consists of Water (0.1% NH_4OH) and MeOH. The gradient used starts a 0% MeOH: 90% Water (0.1% NH_4OH) and moves to 90% MeOH : 10% Water (0.1% NH_4OH) over 7 minutes. There is a one minute wash of the column using 100% MeOH for one minute, until eight minutes and then original conditions return at 8.1 minutes to 8.5

Example 886

4-fluoro-7-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,3-benzoxazol-2(3H)-one

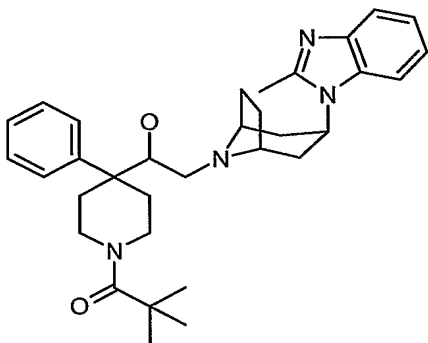


Prepared from a mixture of 4-fluoro-2-oxo-2,3-dihydro-1,3-benzoxazole-7-carboxylic acid (9.8 mg, 0.05 mmol, 1 equiv), endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride (25 mg, 0.05 mmol, 1 equiv), DIEA (36 μ L, 0.2 mmol, 4 equiv) and HATU (19 mg, 0.05 mmol, 1 equiv) following the general procedure for 2,4-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide (example 880). The crude product was purified by prep HPLC (HPLC Method C) to provide 4-fluoro-7-[(4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenyl-1-piperidinyl)carbonyl]-1,3-benzoxazol-2(3H)-one as a white solid (5 mg, 17% yield).

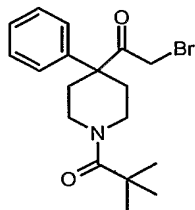
NMR (400 MHz, CDCl_3) δ 7.51-7.34 (m, 1H), 7.26-7.22 (m, 1H), 7.16-7.07 (m, 4H), 4.53 (m, 1H), 3.94 (m, 1H), 3.5-3.1 (m, 6H), 2.54-2.05 (m, 12H), 1.96-1.59 (m, 6H). ES-LCMS m/z 608.17 (M+H).

Example 887

1-{1-(2,2-dimethylpropanoyl)-4-phenylpiperidin-4-yl}-2-[3-(2-methyl-1 *H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethanol



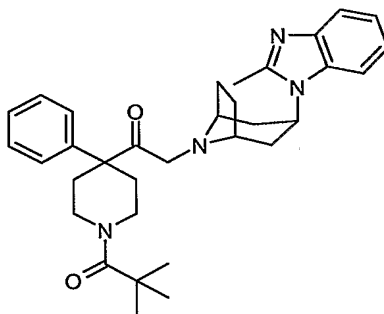
Synthesis of 2-bromo-1-[1-(2,2-dimethylpropanoyl)-4-phenylpiperidin-4-yl]ethanone



To a suspension of 4-acetyl-4-phenyl piperidine hydrochloride (20.8mmol) in DCM (200ml) was added TEA (541.1mmol) and the mixture was stirred under an inert atmosphere for 10 minutes. Pivaloyl chloride (22.8mmol) was added and the mixture was stirred until HPLC analysis indicated that the reaction was complete. Water and EtOAc were added. The ethyl acetate layer was separated and washed with satd. NaHCO₃, water, brine and dried (Na₂SO₄). Removal of solvent under vacuum gave the intermediate ketone, which was used directly in the next step. ¹H NMR (400 MHz, DMSO d-6) 7.21-7.40 (m, 5 H), 3.77-3.82 (dt, 2 H), 3.14-3.21 (t, 2 H), 2.45-2.51 (m, 2H), 2.31-2.41 (d, 2H), 1.20 (s, 2H), 1.14 (s, 9H). LCMS *m/z* (M+H) calcd: 287.48 obsd: 288.44. To a solution of 1-[1-(2,2-dimethylpropanoyl)-4-phenylpiperidin-4-yl]ethanone in MeOH (125ml) at 0° C. Br₂ was added (24.5mmol) dropwise over 10 minutes. The mixture was stirred 12 hrs. at room temperature under an inert atmosphere. H₂O (20ml) was added and the resulting mixture was stirred for

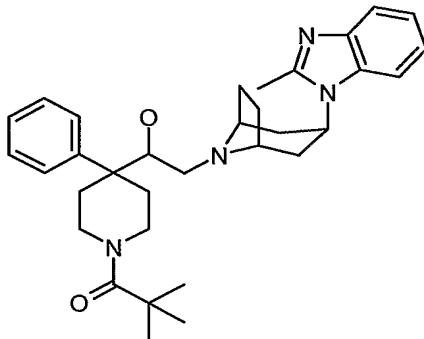
an additional 0.5 hr. Et₂O and water (250ml 1:1) were added, the organic layer was washed with water, satd. K₂CO₃ solution, dried (Na₂SO₄) and the solvent was removed *in-vacuo* to give **2** as a lightly colored powder (7g, 92%). HPLC: rt=5.26 min. This compound was used directly in the following step.

The synthesis of 1-{1-(2,2-dimethylpropanoyl)-4-phenylpiperidin-4-yl}-2-[3-(2-methyl-1 *H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethanone



To the amine IV in scheme III (3mmol) in Et₂O was added TEA (17.9mmol) and the reaction mixture was stirred under inert atmosphere for 1hr. Next, 2-bromo-1-[1-(2,2-dimethylpropanoyl)-4-phenylpiperidin-4-yl]ethanone (2.7mmol) in Et₂O (20ml) was added and the resulting mixture was stirred overnight. Benzene (50ml) and TEA (14.3mmol) were added to the reaction and the whole was heated to 90⁰ C overnight. The reaction was cooled to room temperature and concentrated *in-vacuo*. The crude material in DCM was washed with brine, and water and then dried (Na₂SO₄). Concentration under vacuum gave 1-{1-(2,2-dimethylpropanoyl)-4-phenylpiperidin-4-yl}-2-[3-(2-methyl-1 *H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethanone, which was purified by silica gel chromatography (DCM: MeOH; 9.5: 0.5) to give (400mg, 30%) as a white powder. ¹H NMR (400 MHz, CDCl₃), 7.67 (d, 1H), 7.29-7.42 (m, 6H), 7.08-7.22 (m, 2H), 4.63-4.78 (m, 1H), 4.08-4.18 (m, 3H), 3.28-3.39 (m, 2H), 3.12-3.23 (m, 2H), 3.08-3.10 (s, 2H), 2.61 (s, 3H), 2.50(m, 2H), 2.39-2.40 (m, 2H), 2.10 (s, 2H), 1.84-1.90 (m, 2H), 1.61 (s, 3H), 1.28 (s, 9H). LCMS *m/z* (M+H) calcd: 526.72, obsd: 527.45

The synthesis of 1-{1-(2,2-dimethylpropanoyl)-4-phenylpiperidin-4-yl}-2-[3-(2-methyl-1 *H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethanol



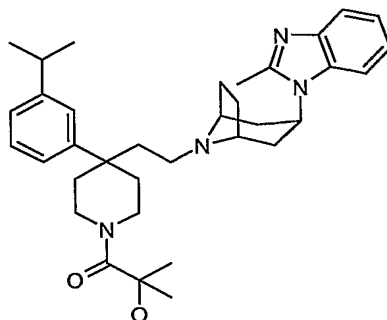
To a solution of 1-{1-(2,2-dimethylpropanoyl)-4-phenylpiperidin-4-yl}-2-[3-(2-methyl-1 *H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethanone (30mg) in MeOH (5ml) was added NaBH₄ (0.9mmol) and the reaction mixture was stirred overnight. Satd. NaHCO₃ was added and the product was extracted with DCM (3x). The organics were dried (Na₂SO₄). Removal of solvent under of vacuum gave the desired product 4 as a white solid. ¹H NMR (CDCl₃) 7.64-7.70 (m, 1H), 7.35-7.41 (m, 4H), 7.29-7.30 (m, 1H), 7.11 (m, 2H), 4.49-4.62 (m, 1H), 4.22-4.30 (s, 2H), 3.50-3.60 (dd, 1H), 3.34 (t, 1H), 3.15 (t, 1H), 2.90-2.77 (q, 2H), 2.51 (s, 3H), 2.34-2.44 (m, 3H), 2.22 (d, 1H), 2.1 (dd, 1H), 1.94 (m, 4H), 1.90 (m, 1H), 1.71-1.80 (m, 3H), 1.25 (s, 9H). HPLC (3.483 min, 100%)

HPLC : ZORBAX (2.1x50mm; 3.5micron), T=40°C; ACN/water+0.05%TFA; 0-to-95% over 8min.

Example 888

3-(4-(3-isopropylphenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazole-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)2,2-dimethyl-3-oxopropan-1-ol

622

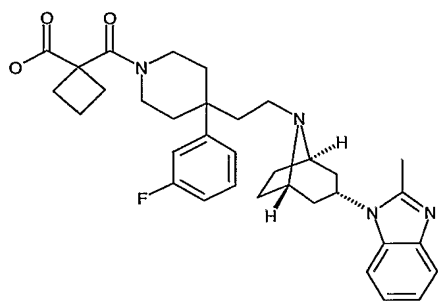


This compound was prepared from 3-isopropyl phenylmagnesium bromide and 16a according to the procedure described in example 16. To a solution of 3-hydroxy-2,2-dimethylpropanoic acid (0.14mmol), DIEA (1.7mmol) and HATU (0.14mmol) in DMF was added 1-(8-{2-[4(-3-isopropylphenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole hydrochloride (0.13mmol) in the same solvent and stirring was continued overnight. The reaction mixture was diluted with EtOAc, and washed with NaHCO₃, water, and satd. brine and dried (Na₂SO₄). The solvent was removed *in-vacuo* and the crude material was purified by HPLC to 1 as a clear film. H NMR (400MHz, CDCl₃) 9.72 (s, 2H), 8.48 (s, 1H), 7.64 (d, 1H), 7.04-7.36 (m, 8H), 4.74 (t, 1H), 3.19-3.32 (m, 4H), 2.88-2.97 (m, 3H), 2.60 (s, 3H), 2.43-2.47 (d, 4H), 2.37 (s, 2H), 1.86-2.33 (m, 10H), 1.77 (d, 2H), 1.26-1.28 (d, 6H). LCMS *m/z* (M+H) calc: 556.79, obsd: 557.79.

Example 889

Preparation of

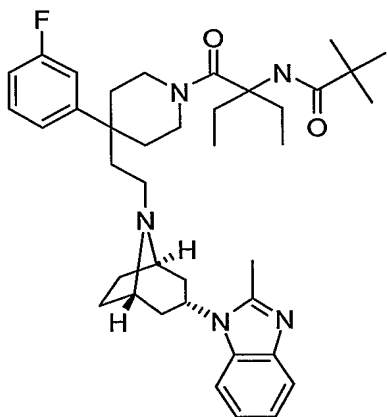
1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-cyclobutanecarboxylic acid



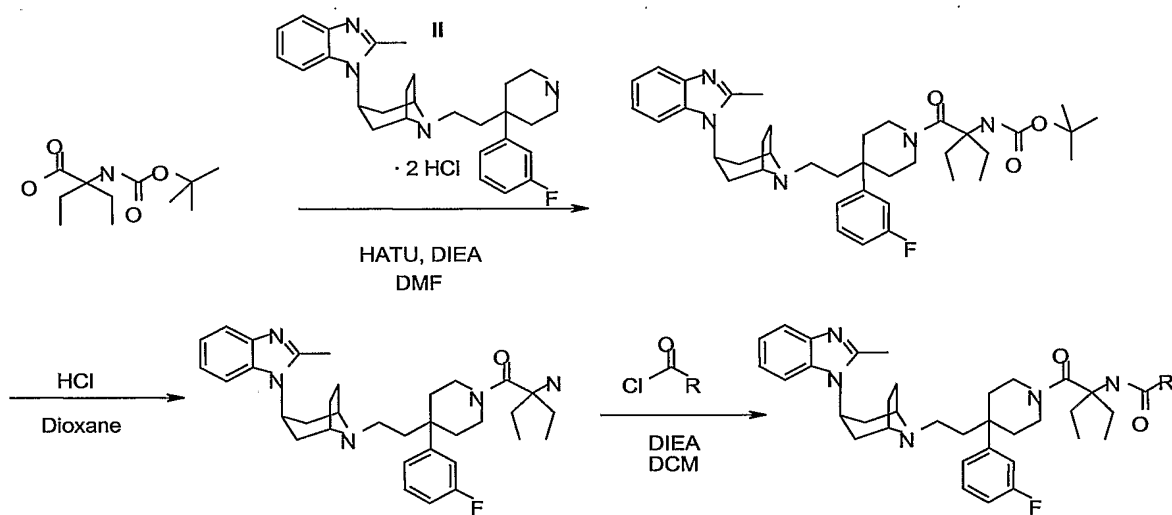
1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-cyclobutanecarboxylic acid was obtained from a solution of 1-(ethoxycarbonyl)cyclobutane carboxylic acid (0.031 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5 to produce 1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-cyclobutanecarboxylic acid ethyl ester. The ester (0.100 g, 0.167 mmol), 5 N NaOH (10 ml) and ethanol (4 ml) was stirred at 90°C for 3 hrs. The reaction was evaporated to dryness and residue was suspend in water (10 ml) and neutralized with 1N HCl. The aqueous layer was extracted with ethyl acetate (3 x 10 ml). The organic layer was dried using magnesium sulfate and concentrated down to form the title compound as a white solid (0.078 g, 81%). ¹H NMR (400 MHz, CDCl₃), 7.70 (m, 1H), 7.32-7.16 (m, 4H), 7.04 (m, 1H), 6.97-6.92 (m, 2H), 4.74 (m, 1H), 4.24-3.99 (m, 4H), 3.44-3.40 (m, 1H), 3.30 (br, 2H), 3.19 (m, 1H), 3.10 (m, 1H), 2.77 (m, 1H), 2.59 (s, 3H), 2.44-2.28 (br, 4H) 2.10-2.00 (m, 4H), 1.91-1.78 (m, 8H), 1.66 (m, 2H). ES-LCMS *m/z* 573 (M+1).

Example 890Preparation of

N-[1-Ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-2,2-dimethyl-propionamide



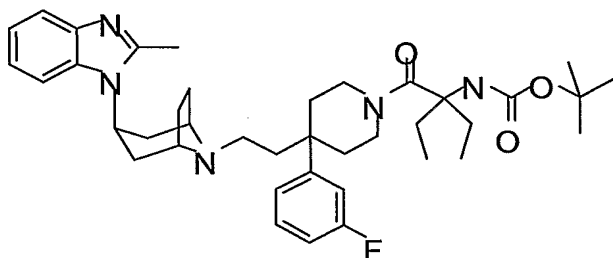
Prepared as outlined below.



Example 890: R = t-butyl

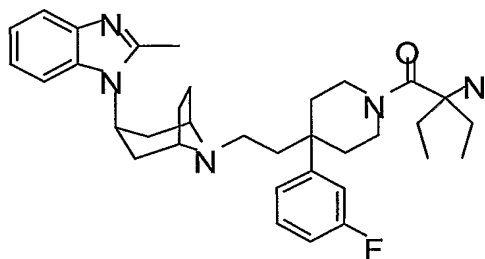
Example 891: R = methyl

Preparation of [1-Ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester



A mixture of 2-tert-Butoxycarbonylamino-2-ethyl-butyric acid (0.291 g, 1.35 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride (0.700 g, 1.35 mmol), and HATU (0.514 g, 1.35 mmol) following the procedure outlined in example 5. Obtained 0.712 g (80%) of an oil. ES-LCMS m/z 660(M+1).

Preparation of 2-Amino-2-ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one



[1-Ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester was treated with 4N HCl (20ml) in dioxane and then solvent was removed in vacuo. Residue was dissolved in water neutralized and extracted with EtOAcX3 to yield 0.600 g (99%) of the deprotected amine product as an oil. ES-LCMS m/z 560(M+1).

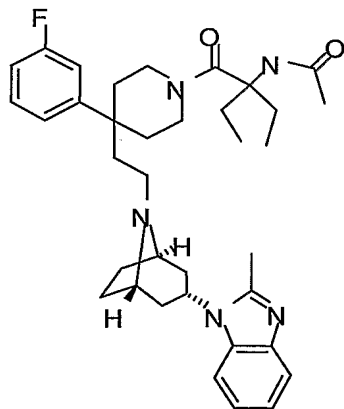
Preparation of title example 890:

A solution of 2-Amino-2-ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-butan-

1-one (0.100 g, 0.178 mmol), 2,2-Dimethyl-propionyl chloride (0.021 g, 0.178 mmol) and DIEA (0.069 g, 0.534 mmol) were stirred at room temperature in DCE (3 ml) for 2 hours. Solvent was removed and compound was purified by RP-HPLC to yield 0.065 g (57%). ¹H NMR (400 MHz, CDCl₃) 7.82 (s, 1H), 7.67 (m, 1H), 7.36 (m, 1H), 7.29 (m, 1H), 7.16 (m, 2H), 7.09 (m, 1H), 6.99 (m, 1H), 4.60 (m, 1H), 4.07 (br, 2H), 3.32-3.23 (m, 4H), 2.79 (m, 2H), 2.57 (s, 3H), 2.36 (m, 2H), 2.21 (m, 2H), 1.92 (m, 6H), 1.80 (m, 4H), 1.65 (m, 6H), 1.23 (s, 9H) 0.76 (br, 5H). ES-LCMS *m/z* 644(M+1).

Example 891

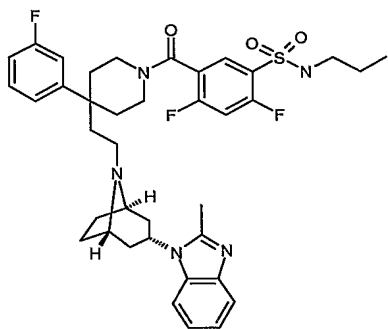
Preparation of N-[1-Ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide



A solution of 2-Amino-2-ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one (0.100 g, 0.178 mmol), acetyl chloride (0.014 g, 0.178 mmol) and DIEA (0.069 g, 0.534 mmol) were stirred at room temperature in DCM (3 ml) for 2 hours. Solvent was removed and compound was purified by RP-HPLC to yield 0.072 g (67%). ¹H NMR (400 MHz, CDCl₃) 7.67 (m, 1H), 7.40-7.29 (m, 2H), 7.18 (m, 2H), 7.09 (m, 1H), 6.99 (m, 2H), 4.60 (m, 1H) 4.04 (br, 2H), 3.32-3.23 (m, 4H), 2.74 (m, 2H), 2.57(s, 3H), 2.36 (m, 2H), 2.20 (m, 2H), 2.01 (s, 3H), 1.92 (m, 6H), 1.82-1.63 9 (m, 10H), 0.78 (br, 5H). ES-LCMS *m/z* 602(M+1).

Example 892

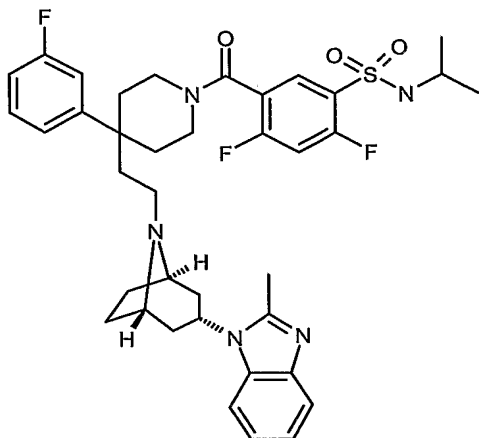
Preparation of 2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-N-propyl-benzenesulfonamide



2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-N-propyl-benzenesulfonamide (0.068 g, 53%) was obtained from a solution of 2,4-Difluoro-5-propylsulfamoyl-benzoic acid (ACID 34) (0.050 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5. ¹H NMR (400MHz, CDCl₃) 7.63 (m, 1H), 7.36-7.28 (m, 3H), 7.15 (m, 2H), 7.08 (m, 1H), 6.96 (m, 3H), 4.60 (m, 1H), 4.22 (m, 1H), 3.37 (m, 2H), 3.23 (m, 3H), 2.98 (m, 2H) 2.56 (s, 3H), 2.38 (m, 3H), 2.12 (m, 1H), 1.93- 1.82 (m, 11H), 1.62 (m, 2H), 1.51 (m, 2H), 0.89 (m, 3H). ES-LCMS *m/z* 708(M+1).

Example 893

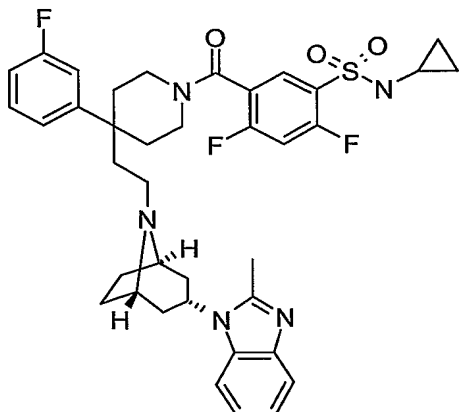
Preparation of 2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-N-isopropyl-benzenesulfonamide



2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-N-isopropyl-benzenesulfonamide (0.071 g, 55%) was obtained from a solution of 2,4-Difluoro-5-isopropylsulfonylbenzoic acid (ACID 35) (0.050 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5. ¹H NMR (400MHz, CDCl₃) 7.96 (m, 1H), 7.66 (m, 1H), 7.36-7.29 (m, 2H), 7.17 (m, 2H), 7.08 (m, 1H), 6.98 (m, 3H), 4.91 (m, 1H), 4.61 (m, 1H), 4.23 (m, 1H), 3.54 (m, 1H), 3.37 (m, 1H), 3.25 (m, 3H), 2.56 (s, 3H), 2.41-2.28 (m, 3H), 2.14 (m, 1H), 1.96-1.74 (m, 10H), 1.63 (m, 2H), 1.12 (m, 6H). ES-LCMS *m/z* 708(M+1).

Example 894

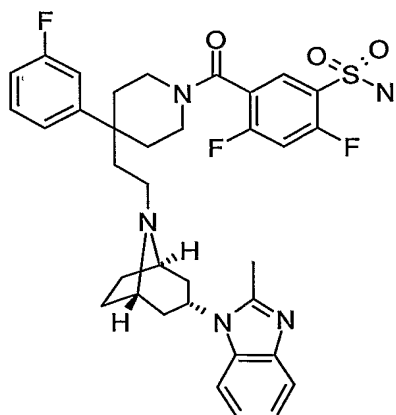
Preparation of N-Cyclopropyl-2,4-difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-benzenesulfonamide



N-Cyclopropyl-2,4-difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methylbenzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-benzenesulfonamide (0.081 g, 64%) was obtained from a solution of 5-Cyclopropylsulfamoyl-2,4-difluoro-benzoic acid (ACID 36) (0.050 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5. ¹H NMR (400MHz, CDCl₃) 8.01 (m, 1H), 7.66 (m, 1H), 7.37-7.29 (m, 2H), 7.16 (m, 2H), 7.08-6.90 (m, 4H), 5.47 (m, 1H), 4.64 (m, 1H), 4.24 (m, 1H), 3.37 (m, 2H), 3.27-3.17 (m, 3H), 2.57 (s, 3H), 2.42-2.29 (m, 4H), 2.13 (m, 1H), 1.94-1.78 (m, 10 H), 1.65 (m, 2H), 0.65 (m, 4H). ES-LCMS *m/z* 706(M+1).

Example 895

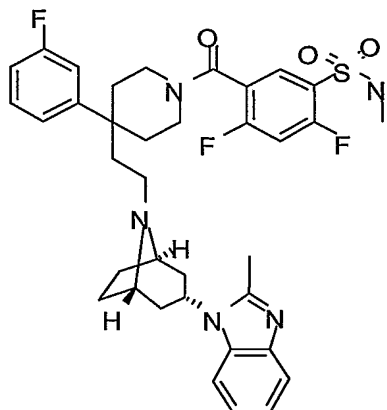
Preparation of 2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methylbenzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-benzenesulfonamide



2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-benzenesulfonamide (0.059 g, 49%) was obtained from a solution of 2,4-Difluoro-5-sulfamoyl-benzoic acid (ACID 31) (0.043 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo [3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5. ¹H NMR (400MHz, CDCl₃) 7.98 (m, 1H), 7.66 (m, 1H), 7.37-7.29 (m, 2H), 7.18-6.97 (m, 6H), 5.35 (m, 1H), 4.61 (m, 1H), 4.20 (m, 1H), 3.38 (m, 2H), 3.25 (m, 3H), 2.56 (s, 3H), 2.44-2.27 (m, 3H), 2.14 (m, 1H), 1.96-1.79 (m, 10 H), 1.66 (m, 2H). ES-LCMS *m/z* 666(M+1).

Example 896

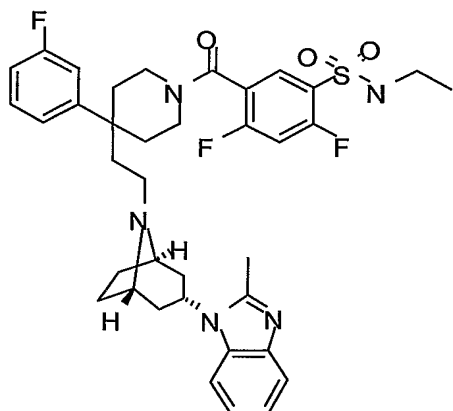
Preparation of 2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-N-methyl-benzenesulfonamide



2,4-Difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-N-methyl-benzenesulfonamide (0.063 g, 51%) was obtained from a solution of 2,4-Difluoro-5-methylsulfonyl-benzoic acid (ACID 32) (0.045 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo [3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5. ¹H NMR (400MHz, CDCl₃) 7.98 (m, 1H), 7.68 (m, 1H), 7.36 (m, 1H), 7.29 (m, 1H), 7.19 (m, 2H), 7.09 (m, 1H), 6.99 (m, 3H), 4.82 (m, 1H), 4.63 (m, 1H), 4.23 (m, 1H), 3.39 (m, 2 H), 3.30 (m, 2H), 3.22 (m, 1H), 2.74 (s, 3H), 2.59 (s, 3H), 2.42 (m, 2H), 2.29 (m, 2H), 2.17 (m, 2H), 1.98-1.71 (m, 10H), 1.67 (m, 2H). ES-LCMS *m/z* 680(M+1).

Example 897

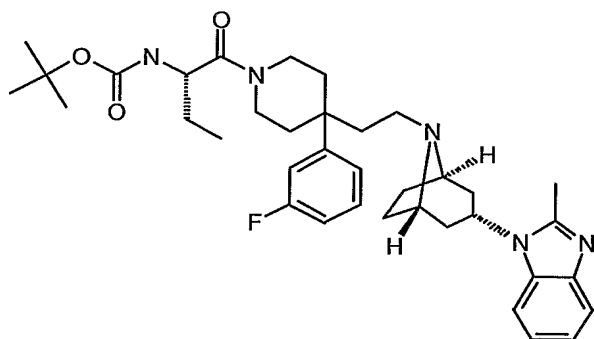
Preparation of N-Ethyl-2,4-difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-benzenesulfonamide



Preparation of N-Ethyl-2,4-difluoro-5-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-benzenesulfonamide (0.067 g, 54%) was obtained from a solution of 5-Ethylsulfamoyl-2,4-difluoro-benzoic acid (ACID 33) (0.047 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo [3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5. ¹H NMR (400MHz, CDCl₃) 7.98 (m, 1H), 7.68 (m, 1H), 7.39 (m, 1H), 7.31 (m, 1H), 7.18 (m, 2H), 7.09 (m, 1H), 6.98 (m, 3H), 4.81 (br, 2H), 4.20 (m, 1H), 3.38 (m, 4H), 3.21 (m, 1H), 3.16 (m, 2H), 2.61 (s, 3H), 2.44 (m, 2H), 2.31 (m, 1H), 2.19 (m, 1H), 2.02-1.61 (m, 12H), 1.16 (m, 3H). ES-LCMS *m/z* 694(M+1).

Example 898

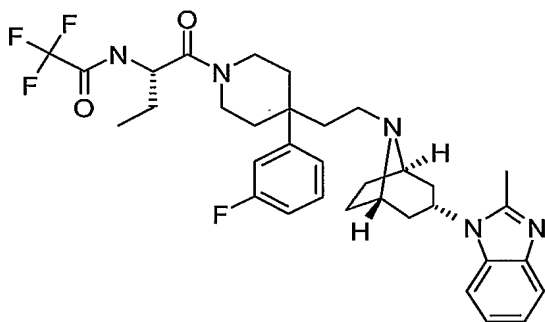
Preparation of [1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester



[1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester(0.580 g, 66%) was obtained as an oil from 2-tert-Butoxycarbonylamino-butyric acid (0.298 g, 1.40 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride (0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS m/z 632(M+1).

Example 899

Preparation of 2,2,2-Trifluoro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide

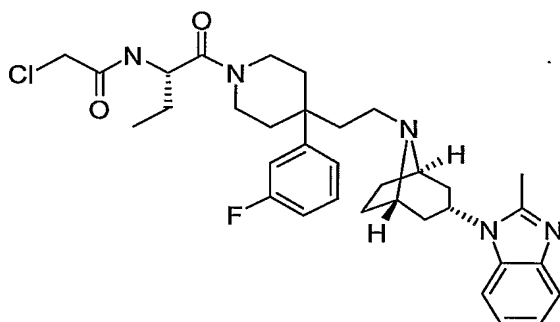


2,2,2-Trifluoro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide was obtained from treating [1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester(0.580 g, 0.92 mmol) with HCl as outlined in the procedure for example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one(0.488 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo [3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one(0.049 g, 0.09 mmol, trifluoroaceticanhydride (0.019 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure

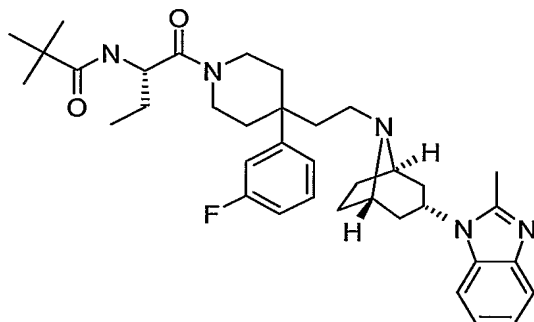
outlined in example 890 to give the title compound, 2,2,2-Trifluoro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide(0.034 g, 60%) as an oil. ES-LCMS m/z 628(M+1).

Example 900

Preparation of 2-Chloro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide

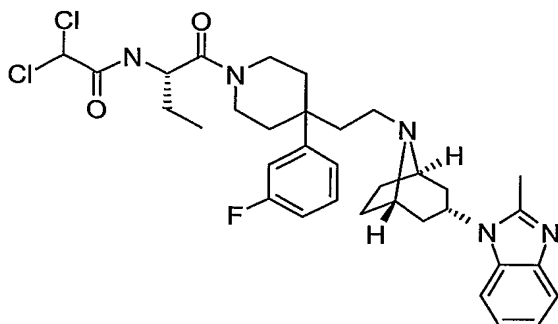


2-Chloro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide was obtained from treating [1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester(0.580 g, 0.92 mmol) with HCl as outlined in the procedure for example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one(0.488 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo [3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one(0.049 g, 0.09 mmol, Chloro-acetyl chloride (0.010 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in example 890 to give the title compound, 2-Chloro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide (0.024 g, 44%) as an oil. ES-LCMS m/z 608(M+1).

Example 901Preparation of N-[1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-2,2-dimethyl-propionamide

N-[1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-2,2-dimethyl-propionamide was obtained from treating [1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester (0.580 g, 0.92 mmol) with HCl as outlined in the procedure for example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one (0.488 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one (0.049 g, 0.09 mmol), 2,2-Dimethyl-propionyl chloride (0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in example 890 to give the title compound, N-[1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-2,2-dimethyl-propionamide (0.030 g, 54%) as an oil. ES-LCMS m/z 616(M+1).

Example 892Preparation of 2,2-Dichloro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide

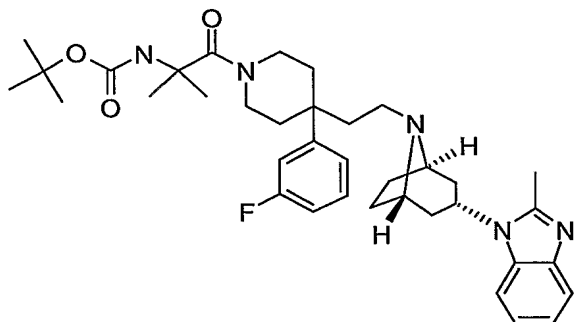


2,2-Dichloro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide was obtained from treating [1-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-carbamic acid tert-butyl ester (0.580 g, 0.92 mmol) with HCl as outlined in the procedure for example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one (0.488 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo [3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one (0.049 g, 0.09 mmol, Dichloro-acetyl chloride (0.013 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in example 890 to give the title compound, 2,2-Dichloro-N-[1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidine-1-carbonyl)-propyl]-acetamide (0.039 g, 67%) as an oil. ES-LCMS m/z 642(M+1).

Example 893

Preparation of [2-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester

637

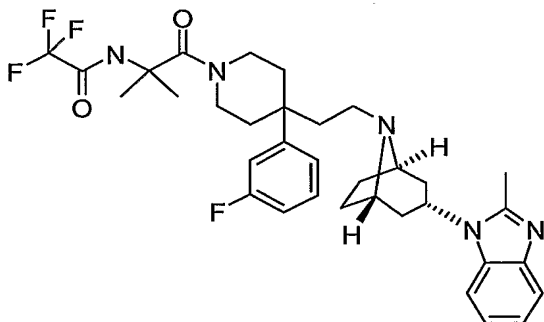


2-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester

(0.610 g, 69%) was obtained as a oil from 2-tert-Butoxycarbonylamino-2-methyl-propionic acid (0.284 g, 1.40 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzoimidazole dihydrochloride(0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS m/z 632(M+1).

Example 904

Preparation of 2,2,2-Trifluoro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide



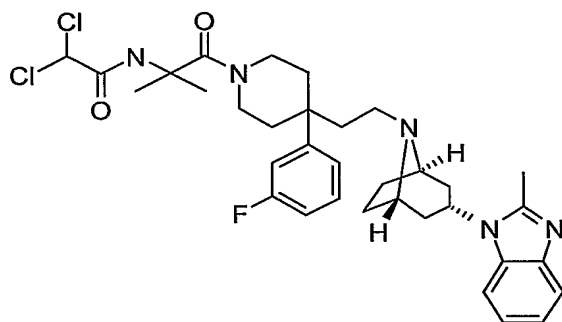
2,2,2-Trifluoro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide

was obtained from treating 2-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-

dimethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester (0.610 g, 0.97 mmol) with HCl as outlined in the procedure in example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-2-methyl-propan-1-one (0.510 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-2-methyl-propan-1-one (0.050 g, 0.09 mmol, trifluoroacetic anhydride (0.019 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in example 890 to give the title compound, 2,2,2-Trifluoro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide (0.024 g, 42%) as an oil. ES-LCMS m/z 628(M+1).

Example 905

Preparation of 2,2-Dichloro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide



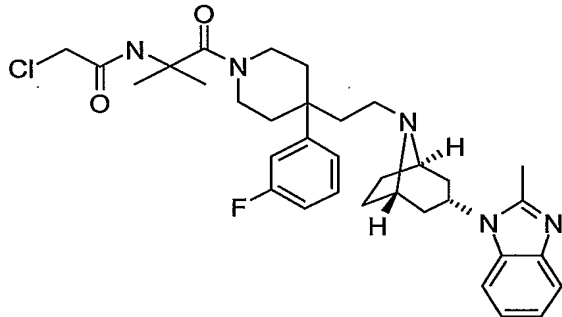
2,2-Dichloro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide

was obtained from treating 2-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester (0.610 g, 0.97 mmol) with HCl as outlined in the procedure for example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-

yl]-ethyl}-piperidin-1-yl)-2-methyl-propan-1-one (0.510 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-2-methyl-propan-1-one (0.050 g, 0.09 mmol), Dichloro-acetyl chloride(0.013 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in example 890 to give the title compound, 2,2-Dichloro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide(0.028 g, 48%) as an oil. ES-LCMS m/z 642(M+1).

Example 906

Preparation of 2-Chloro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide

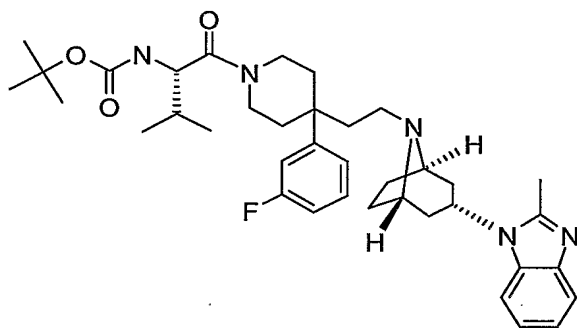


2-Chloro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide was obtained from treating 2-(4-(3-Fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-carbamic acid tert-butyl ester (0.610 g, 0.97 mmol) with HCl as outlined in the procedure for Example 890 to form 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-2-methyl-propan-1-one(0.510 g, 99%). 2-Amino-1-(4-(3-fluoro-phenyl)-4-{2[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-2-methyl-propan-1-one (0.050 g, 0.09 mmol, Chloro-acetyl chloride(0.010 g, 0.09 mmol) and DIEA (0.034 g,

0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2-Chloro-N-[2-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzimidazol-1-yl)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethyl}-piperidin-1-yl)-1,1-dimethyl-2-oxo-ethyl]-acetamide (0.027 g, 49%) as an oil. ES-LCMS m/z 608 (M+1).

Example 907

Preparation of 1,1-dimethylethyl {(1S)-1-[4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}carbamate

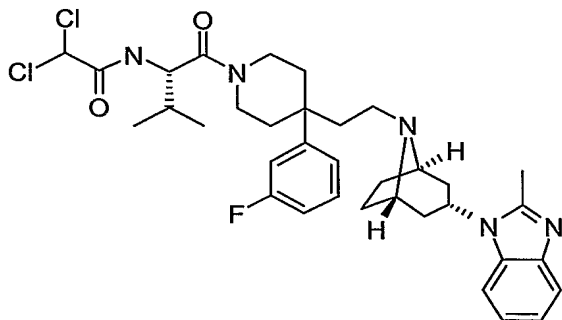


1,1-dimethylethyl {(1S)-1-[4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}carbamate (0.614 g, 68%) was obtained as a oil from *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-L-valine (0.303 g, 1.40 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.725 g, 1.40 mmol) and HATU (0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS m/z 648(M+1).

Example 908A

Preparation of 2,2-dichloro-N-{(1S)-1-[4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}acetamide

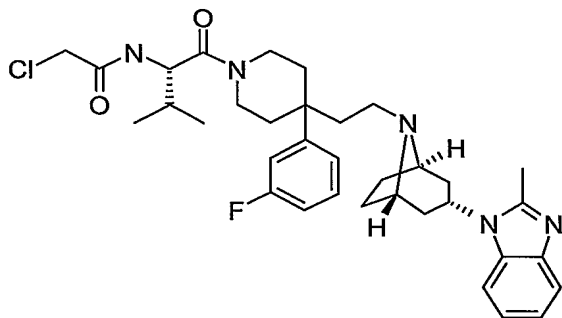
641



2,2-dichloro-*N*-{[(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2-methylpropyl}acetamide was obtained from treating 1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}carbamate (0.614 g, 0.95 mmol) with HCl as outlined in the procedure for Example 890 to form {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}amine (0.512 g, 99%). {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}amine (0.050 g, 0.09 mmol), Dichloro-acetyl chloride (0.013 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2,2-dichloro-*N*-{[(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2-methylpropyl}acetamide (0.031 g, 53%) as an oil. ES-LCMS *m/z* 656 (*M*+1).

Example 908B

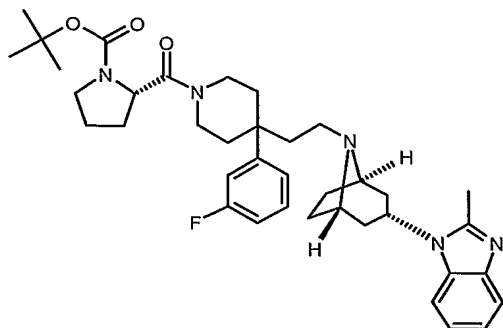
Preparation of 2-chloro-*N*-{[(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2-methylpropyl}acetamide



2-chloro-N-((1S)-1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2-methylpropyl)acetamide was obtained from treating 1,1-dimethylethyl {(1S)-1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}carbamate(0.614 g, 0.95 mmol) with HCl as outlined in the procedure for Example 890 to form {(1S)-1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}amine (0.512 g, 99%). {(1S)-1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2-methylpropyl}amine(0.050 g, 0.09 mmol), Chloro-acetyl chloride(0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2-chloro-N-((1S)-1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2-methylpropyl)acetamide(0.037 g, 66%) as an oil. ES-LCMS m/z 622 (M+1).

Example 909

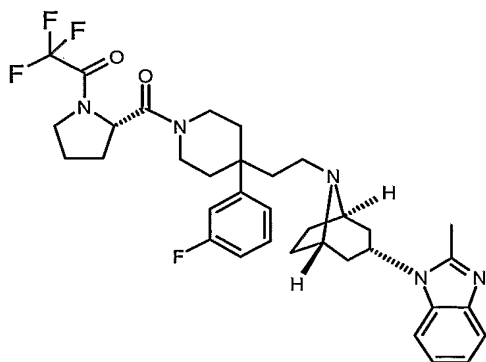
Preparation of 1,1-dimethylethyl (2S)-2-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1-pyrrolidinecarboxylate



1,1-dimethylethyl (2S)-2-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1-pyrrolidinecarboxylate (0.645 g, 72%) was obtained as a oil from 1-[(1,1-dimethylethyl)oxy]carbonyl-L-proline (0.301 g, 1.4 mmol), 1-(8-{2-[4-(3-Fluorophenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.725 g, 1.40 mmol) and HATU (0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS m/z 644(M+1).

Example 910

Preparation of 1-[(1R,5S)-8-(2-{4-(3-fluorophenyl)-1-[1-(trifluoroacetyl)-L-prolyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

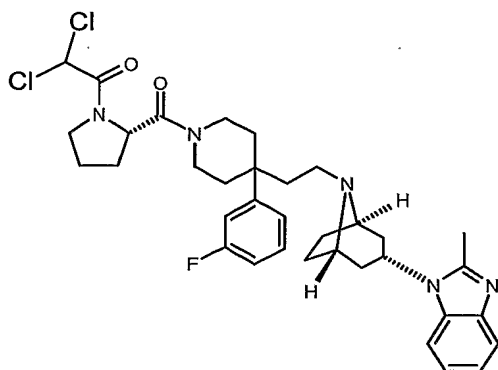


1-[(1R,5S)-8-(2-{4-(3-fluorophenyl)-1-[1-(trifluoroacetyl)-L-prolyl]-4-piperidinyl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole was obtained from treating 1,1-dimethylethyl (2S)-2-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1-pyrrolidinecarboxylate (0.645 g, 1.01 mmol) with HCl

as outlined in the procedure for Example 890 to form 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)-1-*L*-prolyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (0.545 g, 99%). 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)-1-*L*-prolyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (0.050 g, 0.09 mmol), trifluoroacetic anhydride (0.019 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 1-[(1*R*,5*S*)-8-(2-{4-(3-fluorophenyl)-1-[1-(trifluoroacetyl)-*L*-prolyl]-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (0.021 g, 36%) as an oil. ES-LCMS *m/z* 640 (*M*+1).

Example 911

Preparation of 1-((1*R*,5*S*)-8-{2-[1-[1-(dichloroacetyl)-*L*-prolyl]-4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole

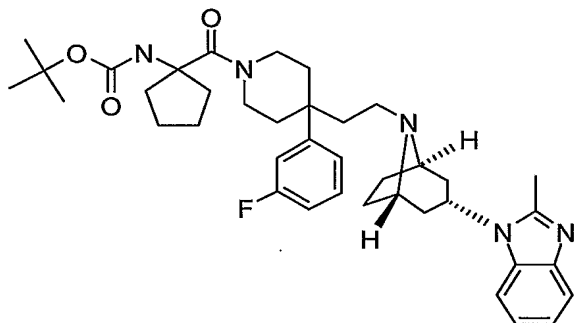


1-((1*R*,5*S*)-8-{2-[1-[1-(dichloroacetyl)-*L*-prolyl]-4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole was obtained from treating 1,1-dimethylethyl (2*S*)-2-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1-pyrrolidinecarboxylate (0.645 g, 1.01 mmol) with HCl as outlined in the procedure for Example 890 to form 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)-1-*L*-prolyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (0.545 g, 99%). 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)-1-*L*-prolyl-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-

benzimidazole(0.050 g, 0.09 mmol), Dichloro-acetyl chloride(0.013 g, 0.09 mmol)and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 1-((1*R*,5*S*)-8-{2-[1-[1-(dichloroacetyl)-L-prolyl]-4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (0.029 g, 49%) as an oil. ES-LCMS *m/z* 654 (M+1).

Example 912

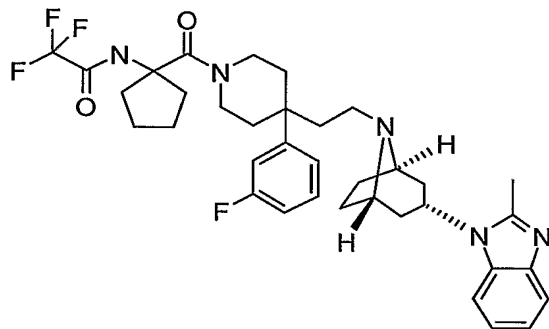
Preparation of 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl)-1-piperidinyl)carbonyl]cyclopentyl}carbamate



1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl)-1-piperidinyl)carbonyl]cyclopentyl}carbamate (0.627 g, 68%) was obtained as a oil from 1-({[(1,1 dimethylethyl)oxy]carbonyl}amino)cyclopentanecarboxylic acid (0.320 g, 1.4 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride(0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 658(M+1).

Example 913

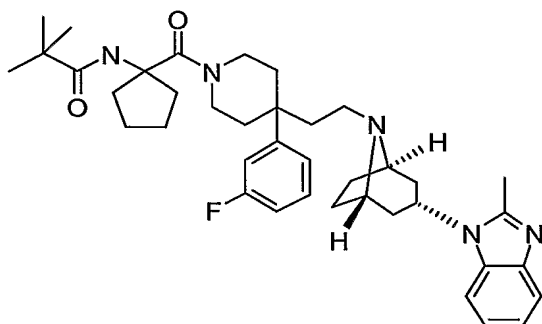
Preparation of 2,2,2-trifluoro-N-{1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}acetamide



2,2,2-trifluoro-N-{1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}acetamide was obtained from treating 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}carbamate (0.627 g, 0.95 mmol) with HCl as outlined in the procedure for Example 890 to form 1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentanamine (0.528 g, 99%). 1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentanamine (0.050 g, 0.09 mmol), trifluoroacetic anhydride (0.019 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2,2,2-trifluoro-N-{1-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}acetamide (0.027 g, 46%) as an oil. ES-LCMS m/z 654 ($M+1$).

Example 914

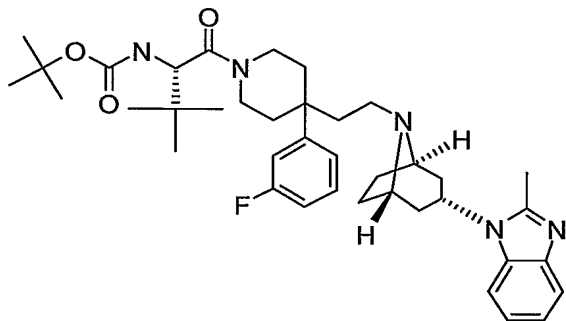
Preparation of *N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}-2,2-dimethylpropanamide



N-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}-2,2-dimethylpropanamide was obtained from treating 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl} carbamate (0.627 g, 0.95 mmol) with HCl as outlined in the procedure for Example 890 to form 1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentanamine (0.528 g, 99%). 1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentanamine (0.050 g, 0.09 mmol), 2,2-Dimethylpropionyl chloride (0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, *N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclopentyl}-2,2-dimethylpropanamide (0.031 g, 54%) as an oil. ES-LCMS *m/z* 642 (*M*+1).

Example 915

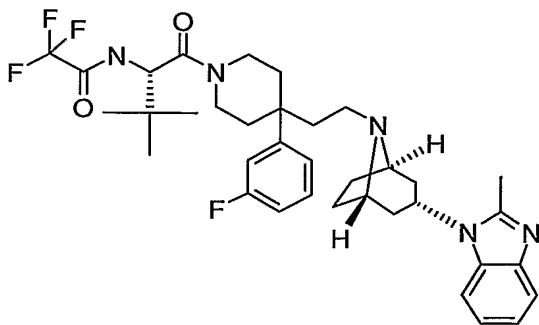
Preparation of 1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}carbamate



1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}carbamate (0.591 g, 64%) was obtained as a oil from *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-methyl-L-valine (0.320 g, 1.4 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (0.725 g, 1.40 mmol) and HATU (0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 660(*M*+1).

Example 916

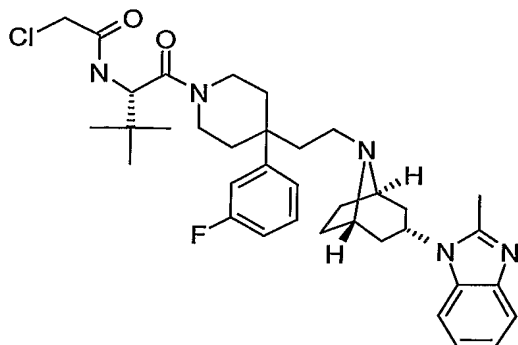
Preparation of 2,2,2-trifluoro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}acetamide



2,2,2-trifluoro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}acetamide was obtained from treating 1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} carbamate (0.591 g, 0.90 mmol) with HCl as outlined in the procedure for Example 890 to form (2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine (0.500 g, 99%). (2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine (0.050 g, 0.09 mmol), trifluoroacetic anhydride (0.019 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2,2,2-trifluoro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} acetamide (0.033 g, 56%) as an oil. ES-LCMS *m/z* 656 (*M*+1).

Example 917

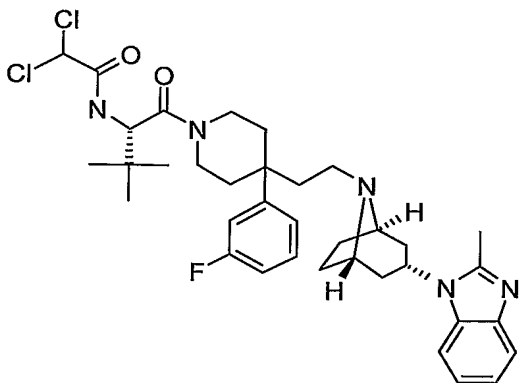
Preparation of 2-chloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}acetamide



2-chloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} acetamide was obtained from treating 1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} carbamate (0.591 g, 0.90 mmol) with HCl as outlined in the procedure for Example 890 to form (2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine (0.500 g, 99%). (2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine (0.050 g, 0.09 mmol), Chloroacetyl chloride (0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2-chloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} acetamide (0.038 g, 66%) as an oil. ES-LCMS *m/z* 636 (*M*+1).

Example 918

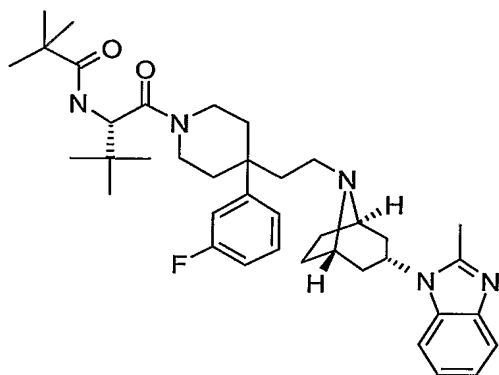
Preparation of 2,2-dichloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}acetamide



2,2-dichloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} acetamide was obtained from treating 1,1-dimethylethyl {(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} carbamate, example 915, (0.591 g, 0.90 mmol) with HCl as outlined in the procedure for Example 890 to form (2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine (0.500 g, 99%). (2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine (0.050 g, 0.09 mmol), Dichloro-acetyl chloride (0.013 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2,2-dichloro-*N*-{(1*S*)-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-2,2-dimethylpropyl} acetamide (0.036 g, 60%) as an oil. ES-LCMS *m/z* 670 (*M*+1).

Example 919

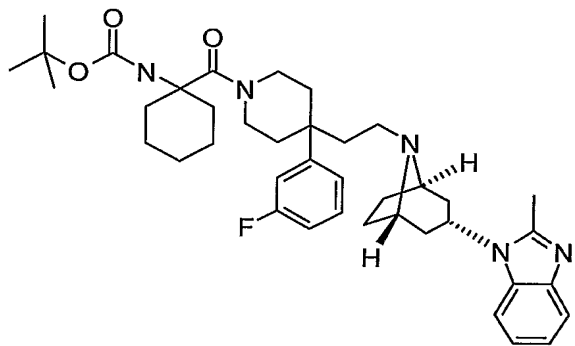
Preparation of *N*-{[1*S*]-1-[4-(3-fluorophenyl)-4-{2-[1*R*,5*S*]-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}-2,2-dimethylpropanamide



N-{(1*S*)-1-[4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}-2,2-dimethylpropanamide was obtained from treating 1,1-dimethylethyl {(1*S*)-1-[4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl} carbamate, example 915, (0.591 g, 0.90 mmol) with HCl as outlined in the procedure for Example 890 to form (2*S*)-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine (0.500 g, 99%). 2*S*-1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-3,3-dimethyl-1-oxo-2-butanamine (0.050 g, 0.09 mmol), 2,2-Dimethylpropionyl chloride (0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, *N*-{(1*S*)-1-[4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-2,2-dimethylpropyl}-2,2-dimethylpropanamide (0.032 g, 55%) as an oil. ES-LCMS *m/z* 644 (*M*+1).

Example 920

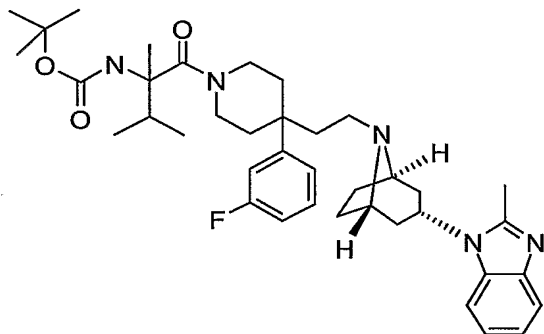
Preparation of 1,1-dimethylethyl {1-[4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclohexyl}carbamate



1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]cyclohexyl}carbamate (0.598 g, 64%) was obtained as a oil from 1-(((1,1-dimethylethyl)oxy)carbonyl)amino)cyclohexanecarboxylic acid (0.320 g, 1.4 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-enzoimidazole dihydrochloride(0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 672(M+1).

Example 921

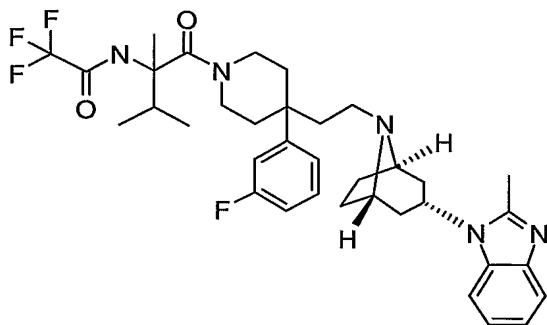
Preparation of 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}carbamate



1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl} carbamate (0.623 g, 67%) was obtained as a oil from *N*-(((1,1-dimethylethyl)oxy)carbonyl)-3-methylisovaline (0.320 g, 1.4 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-enzoimidazole dihydrochloride(0.725 g, 1.40 mmol) and HATU(0.590 g, 1.50 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 660(M+1).

Example 922

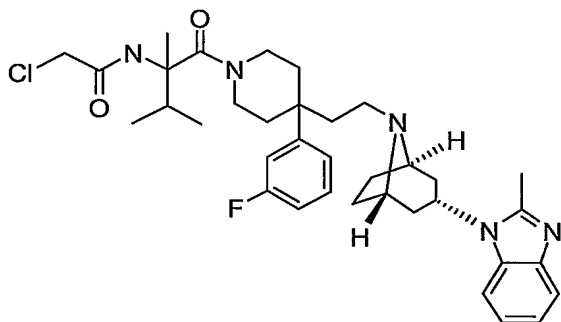
Preparation of 2,2,2-trifluoro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}acetamide



2,2,2-trifluoro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl} acetamide was obtained from treating 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl} carbamate, example 915, (0.623 g, 0.94 mmol) with HCl as outlined in the procedure for Example 890 to form 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine (0.524 g, 99%). 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine (0.050 g, 0.09 mmol), trifluoroacetic anhydride (0.019 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2,2,2-trifluoro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl} acetamide (0.036 g, 61%) as an oil. ES-LCMS *m/z* 656 (*M*+1).

Example 923A

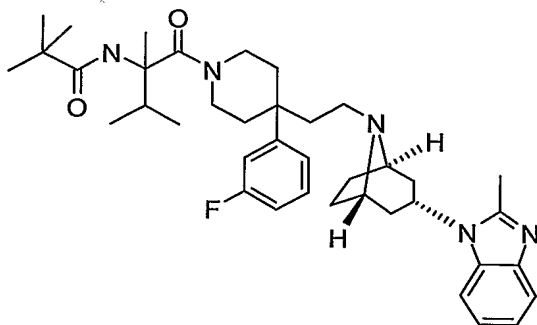
Preparation of 2-chloro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}acetamide



2-chloro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}acetamide was obtained from treating 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}carbamate, example 915, (0.623 g, 0.94 mmol) with HCl as outlined in the procedure for Example 890 to form 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine (0.524 g, 99%). 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine (0.050 g, 0.09 mmol), Chloro-acetyl chloride (0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2-chloro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}acetamide (0.030 g, 52%) as an oil. ES-LCMS *m/z* 636 (*M*+1).

Example 923B

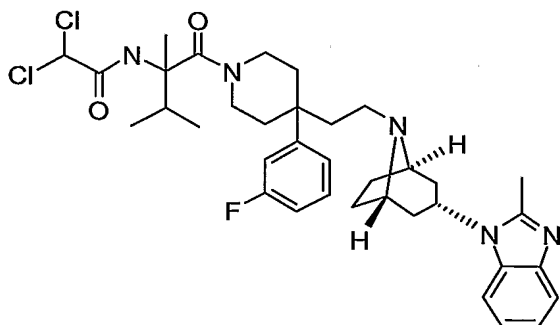
Preparation of *N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}-2,2-dimethylpropanamide



N-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}-2,2-dimethylpropanamide was obtained from treating 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}carbamate, example 915, (0.623 g, 0.94 mmol) with HCl as outlined in the procedure for Example 890 to form 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine (0.524 g, 99%). 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine (0.050 g, 0.09 mmol), 2,2-Dimethyl-propionyl chloride (0.011 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, *N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-1,2-dimethylpropyl}-2,2-dimethylpropanamide (0.039 g, 67%) as an oil. ES-LCMS *m/z* 643 (*M*+1).

Example 924

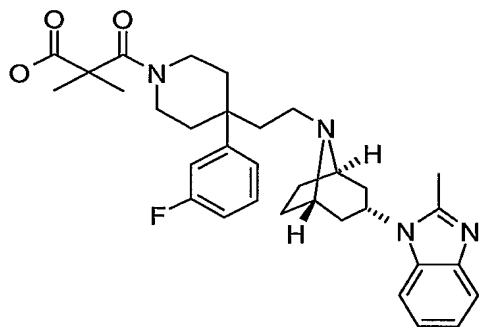
Preparation of 2,2-dichloro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl}acetamide



2,2-dichloro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl} acetamide was obtained from treating 1,1-dimethylethyl {1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-1,2-dimethylpropyl} carbamate, example 915, (0.623 g, 0.94 mmol) with HCl as outlined in the procedure for Example 890 to form 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine (0.524 g, 99%). 1-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,3-dimethyl-1-oxo-2-butanamine (0.050 g, 0.09 mmol), Dichloro-acetyl chloride (0.013 g, 0.09 mmol) and DIEA (0.034 g, 0.534 mmol) were reacted following the procedure outlined in Example 890 to give the title compound, 2,2-dichloro-*N*-{1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]-1,2-dimethylpropyl} acetamide (0.042 g, 69%) as an oil. ES-LCMS *m/z* 643 (*M*+1).

Example 925

Preparation of 3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,2-dimethyl-3-oxopropanoic acid

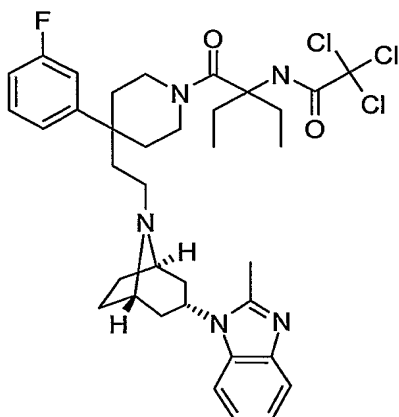


3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,2-dimethyl-3-oxopropanoic acid was obtained from 3-Ethoxy-2,2-dimethyl-3-oxopropanoic acid, Example 628, (0.029 g, 0.18 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-enzoimidazole dihydrochloride (0.075 g, 0.18 mmol), and HATU (0.067 g, 0.18 mmol) following the procedure outlined in example 5 to produce ethyl 3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,2-dimethyl-3-oxopropanoate. Ethyl 3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-2,2-dimethyl-3-oxopropanoate (0.100 g, 0.170 mmol), 5 N NaOH (10 ml) and ethanol (4 ml) was stirred at 90°C for 3 hrs. The reaction was evaporated to dryness and residue was suspend in water (10 ml) and neutralized with 1N HCl. The aqueous layer was extracted with ethyl acetate (3 x 10 ml). The organic layer was dried using magnesium sulfate and concentrated down to form the title compound as a white solid (0.081 g, 85%). ES-LCMS *m/z* 561 (*M*+1).

Example 926

Preparation of 2,2,2-trichloro-*N*-{1-ethyl-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]propyl}acetamide

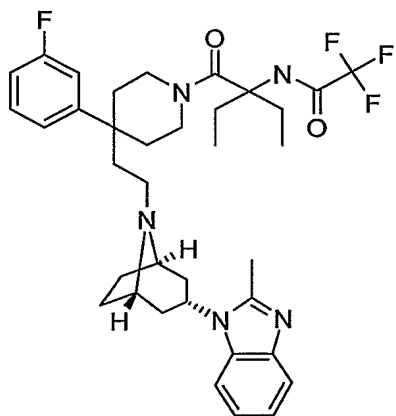
659



2-Amino-2-ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one (0.100 g, 0.178 mmol), trichloroacetyl chloride (0.032 g, 0.178 mmol) and DIEA (0.069 g, 0.534 mmol) as outlined in procedure for procedure for **Example 890** to give title compound, 2,2,2-trichloro-*N*-{1-ethyl-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]propyl}acetamide (0.068 g, 54%). ES-LCMS *m/z* 706 (*M*+1).

Example 927

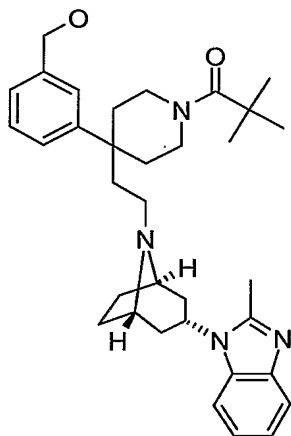
Preparation of *N*-{1-ethyl-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]propyl}-2,2,2-trifluoroacetamide



2-Amino-2-ethyl-1-(4-(3-fluoro-phenyl)-4-{2-[3-(2-methyl-benzoimidazol-1-yl)-8-aza-bicyclo[3.2.1] oct-8-yl]-ethyl}-piperidin-1-yl)-butan-1-one example 890 (0.100 g, 0.178 mmol), trifluoroacetic anhydride (0.038 g, 0.178 mmol) and DIEA (0.069 g, 0.534 mmol) as outlined in procedure for procedure for Example 890 to give title compound, *N*-{1-ethyl-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]propyl}-2,2,2-trifluoroacetamide (0.061 g, 52%). ES-LCMS *m/z* 656 (*M*+1).

Example 928

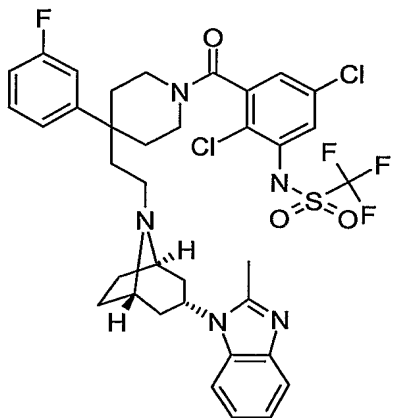
Preparation of [3-(1-(2,2-dimethylpropanoyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-piperidinyl)phenyl]methanol



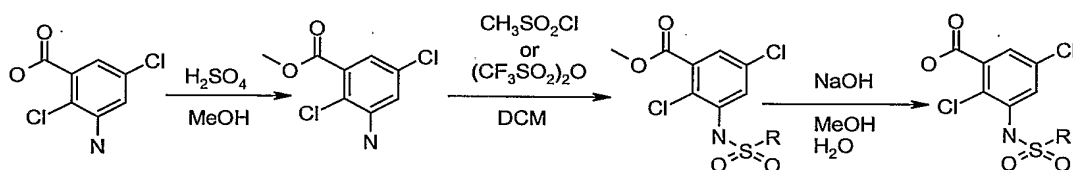
[3-(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-piperidinyl) phenyl]methanol dihydrochloride (0.100 g, 0.188 mmol), Dimethyl-propionyl chloride (0.024 g, 0.188 mmol) and DIEA (0.069 g, 0.534 mmol) were stirred at room temperature in DCM (3 ml) for 2 hours. Solvent was removed and compound was purified by RP-HPLC to give the title compound, [3-(1-(2,2-dimethylpropanoyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-piperidinyl)phenyl]methanol (0.069 g, 71%). ES-LCMS *m/z* 543 (*M*+1).

Example 929

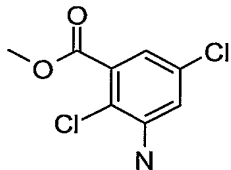
Preparation of *N*-{2,5-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl] phenyl}-1,1,1-trifluoromethanesulfonamide



N-{2,5-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl] phenyl}-1,1,1-trifluoromethanesulfonamide was obtained through procedure outlined in scheme.

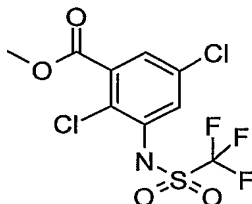


Preparation of methyl 3-amino-2,5-dichlorobenzoate



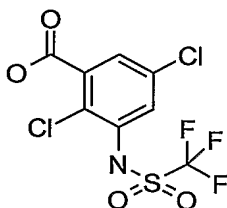
3-amino-2,5-dichlorobenzoic acid(5.00 g, 24.27 mmol) was stirred in methanol(30 ml) at room temperature. Sulfuric Acid(5 ml) was added dropwise. Reaction stirred for 3 hours and was then diluted with water(30 ml) and basified using sodium hydroxide. Mixture was extracted with ethyl acetate x 3. Solvent was removed to afford methyl 3-amino-2,5-dichlorobenzoate(4.20 g, 79%) as a solid.

Preparation of methyl 2,5-dichloro-3-[[trifluoromethyl]sulfonyl]amino}benzoate



methyl 3-amino-2,5-dichlorobenzoate(2.10 g, 9.55 mmol), DIEA(3.0 ml) were stirred in DCM(40 ml) at 0°C. Triflic anhydride(3.90 g, 14.31 mmol) was added dropwise while stirring at 0°C. After 2hrs at 0°C, reaction was allowed to warm to room temperature while stirring overnight. Quenched rxn with saturated NH₄Cl and washed with brine. Organic layer with dried to yeild crude methyl 2,5-dichloro-3-[[trifluoromethyl] sulfonyl]amino}benzoate(4.0 g) which will be carried on.

Preparation of 2,5-dichloro-3-[[trifluoromethyl] sulfonyl]amino}benzoic acid hydrochloride



Crude methyl 2,5-dichloro-3-[[trifluoromethyl] sulfonyl]amino}benzoate(4.0 g) was dissolved in methanol(30 ml) and 4N NaOH(30 ml) was added while stirring at room temperature for 18 hrs. Removed solvent and added 4N HCl(10 ml). Stirred at room temperature for 4hours. Filtered off solid to give 2,5-dichloro-3-[[trifluoromethyl] sulfonyl] amino}benzoic acid hydrochloride in quantitative yield.

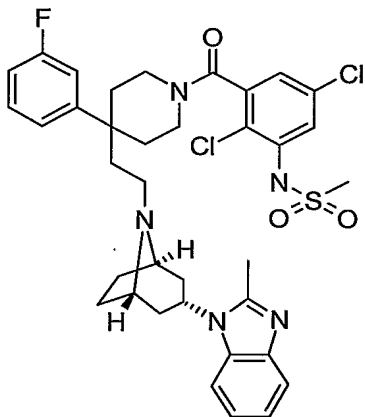
Preparation of example 929

N-{2,5-dichloro-3-[[4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide (0.140 g, 47%)was obtained as a

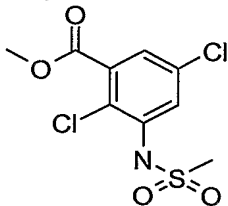
oil from (0.320 g, 1.4 mmol), 2,5-dichloro-3-[[trifluoromethyl] sulfonyl] amino}benzoic acid hydrochloride(0.157 g, 0.46 mmol), 1-(8-{2-[4-(3-Fluorophenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1H-enzoimidazole dihydrochloride(0.200 g, 0.39 mmol) and HATU(0.150 g, 0.46 mmol) following the procedure outlined in example 5. ES-LCMS m/z 766(M+1).

Example 930

Preparation of *N*-{2,5-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl)-1-piperidinyl]carbonyl]phenyl} methanesulfonamide



Preparation of methyl 2,5-dichloro-3-[(methanesulfonyl)amino]benzoate



From common intermediate methyl 3-amino-2,5-dichlorobenzoate following the procedure outlined in scheme. Methyl 3-amino-2,5-dichlorobenzoate(2.10 g, 9.55 mmol), DIEA(3.0 ml) were stirred in DCM(40 ml) at 0°C methanesulfonyl chloride (2.18 g, 19.08 mmol) was added dropwise while stirring at 0°C. After 2hrs at 0°C, reaction was allowed to warm to room temperature while stirring overnight. Quenched rxn with saturated NH₄Cl and

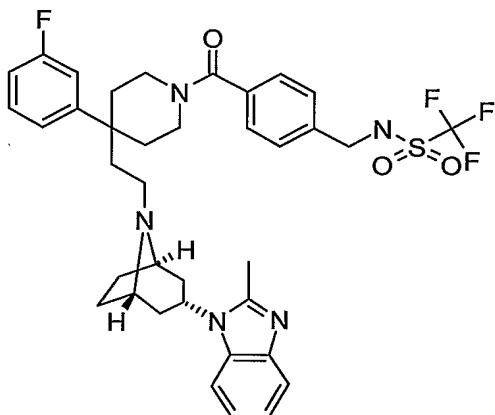
washed with brine. Organic layer with dried to yeild crude methyl 2,5-dichloro-3-[(methylsulfonyl)amino]benzoate(3.10 g) which will be carried on. methyl 2,5-dichloro-3-[(methylsulfonyl)amino]benzoate(3.10 g) was treated with NaOH, methanol following procedure outlined in scheme to form 2,5-dichloro-3-[(methylsulfonyl)amino]benzoic acid hydrochloride (3.53 g).

Preparation of example 930

N-(2,5-dichloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo [3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl} methanesulfonamide (0.127 g, 45%) was obtained as a oil from 2,5-dichloro-3-[(methylsulfonyl)amino]benzoic acid hydrochloride (0.132 g, 0.46 mmol), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzoimidazole dihydrochloride(0.200 g, 0.39 mmol) and HATU(0.150 g, 0.46 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 712(M+1).

Example 931

Preparation of 1,1,1-trifluoro-*N*-(4-{4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl)methyl}methanesulfonamide

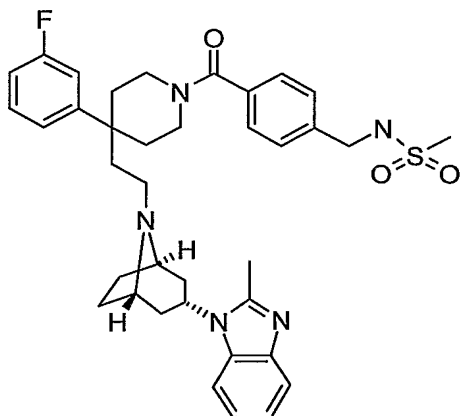


By the procedure outlined in example 929, starting from 4-(aminomethyl)benzoic acid(2.00 g, 13.24 mmol) was treated with sulfuric acid to form methyl 4-(aminomethyl)benzoate(1.20 g, 55%). Methyl 4-

(aminomethyl)benzoate(0.600 g, 3.63 mmol) was treated with triflic anhydride(1.512 g, 4.92 mmol) in DCM(20 ml) to give crude methyl 4-([[(trifluoromethyl)sulfonyl]amino}methyl) benzoate(0.402 g, 37%). Methyl 4-([[(trifluoromethyl) sulfonyl]amino}methyl) benzoate(0.402 g, 1.35 mmol) was treated with NaOH and methanol to give 4-([[(trifluoromethyl)sulfonyl]amino}methyl)benzoic acid hydrochloride(0.380 g, 95%). The title compound, 1,1,1-trifluoro-*N*-({4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl) carbonyl]phenyl}methyl) methanesulfonamide(0.145 g, 52%) was obtained as a oil from 4-([[(trifluoromethyl)sulfonyl]amino}methyl)benzoic acid hydrochloride (0.157 g, 0.46l), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzoimidazole dihydrochloride(0.200 g, 0.39 mmol) and HATU(0.150 g, 0.46 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 712(*M*+1).

Example 932

Preparation of *N*-({4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methyl) methanesulfonamide

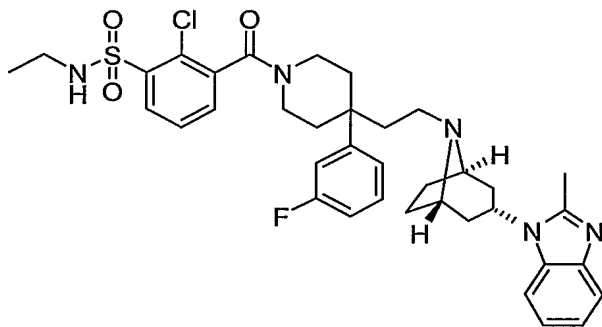


By the procedure outlined in scheme example 929, starting from 4-(aminomethyl)benzoic acid (2.00 g, 13.24 mmol) was treated with sulfuric acid to form methyl 4-(aminomethyl)benzoate(1.20 g, 55%). Methyl 4-(aminomethyl)benzoate (0.600 g, 3.63 mmol) was treated with

methanesulfonyl chloride (0.832 g, 7.26 mmol)) in DCM(20 ml) to give crude methyl 4-[[[(methanesulfonyl)amino] methyl]benzoate(0.398 g, 45%). Methyl 4-[[[(methanesulfonyl)amino]methyl]benzoate(0.398 g, 1.63 mmol) was treated with NaOH and methanol to give 4-[[[(methanesulfonyl)amino]methyl]benzoic acid hydrochloride(0.370 g, 98%). The title compound, *N*-(4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl)-1-piperidinyl)carbonyl]phenyl)methyl) methanesulfonamide (0.128 g, 50%) was obtained as a oil from 4-[[[(methanesulfonyl)amino]methyl]benzoic acid hydrochloride (0.132 g, 0.46l), 1-(8-{2-[4-(3-Fluoro-phenyl)-piperidin-4-yl]-ethyl}-8-aza-bicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride(0.200 g, 0.39 mmol) and HATU(0.150 g, 0.46 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 658(M+1).

Example 933

Preparation of 2-chloro-*N*-ethyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide



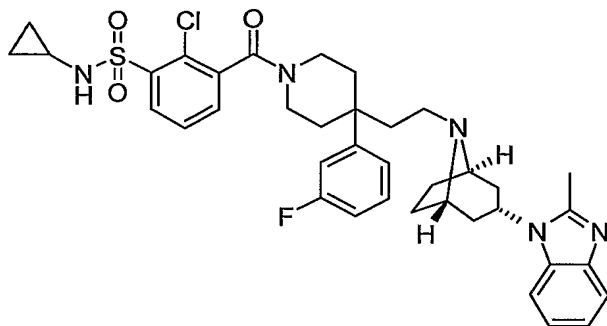
Preparation of 2-chloro-3-[(ethylamino)sulfonyl]benzoic acid. To a solution of methyl 2-chloro-3-(chlorosulfonyl)benzoate (608 mg, 2.26 mmol) and K₂CO₃ (770 mg, 5.6 mmol) in 10 mL benzene was added ethylamine (5.6 mL, 11.2 mmol). Purification of the product provided methyl 2-chloro-3-

[(ethylamino)sulfonyl]benzoate (335 mg, 53%) as a solid. ^1H NMR (400 MHz, CDCl_3), δ 8.24 (dd, 1H, $J = 8.0, 1.7$ Hz), 7.90 (dd, 1H, $J = 7.8, 1.7$ Hz), 7.47 (t, 1H, $J = 7.8$ Hz), 5.14 (t, 1H, $J = 5.9$ Hz), 3.94 (s, 3H), 2.98 (qd, 2H, $J = 7.3, 6.0$ Hz), 1.09 (t, 3H, $J = 7.2$ Hz); ESI-MS 278 (M+H), 300 (M+Na). Methyl 2-chloro-3-[(ethylamino)sulfonyl]benzoate was hydrolyzed using aqueous NaOH to provide 2-chloro-3-[(ethylamino)sulfonyl]benzoic acid as a solid, which was used without further purification. ESI-MS 264 (M+H), 286 (M+Na).

2-chloro-*N*-ethyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide (282 mg, 83%) was obtained as a solid from 2-chloro-3-[(ethylamino)sulfonyl]benzoic acid (51 mg, 0.19 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (117 mg, 0.19 mmol) and HATU (80 mg, 0.21 mmol) following the procedure outlined in example 5. ^1H NMR (400 MHz, CDCl_3), δ 8.12 (m, 1 H), 7.64 (m, 1 H), 7.53-7.40 (m, 2 H), 7.38-7.25 (m, 2 H), 7.14 (m, 2 H), 7.05 (m, 1 H), 7.00-6.92 (m, 2 H), 5.80-5.35 (m, 2 H), 4.52 (m, 1 H), 4.20 (m, 1 H), 3.45-2.87 (m, 7 H), 2.52 (m, 3 H, rotamers), 2.40-1.60 (m, 15 H), 1.1 (m, 3H); ESI-MS 692 (M+H).

Example 934

Preparation of 2-chloro-*N*-cyclopropyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide

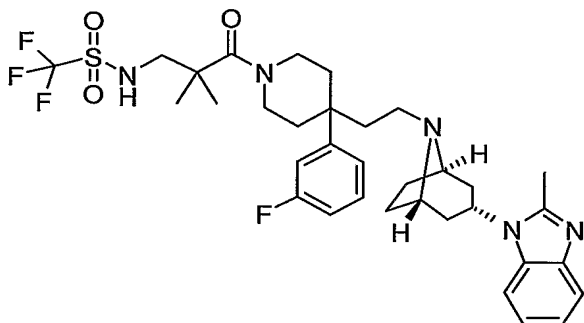


Preparation of 2-chloro-3-[(cyclopropylamino)sulfonyl]benzoic acid. To a solution of methyl 2-chloro-3-(chlorosulfonyl)benzoate (608 mg, 2.26 mmol) and K_2CO_3 (770 mg, 5.6 mmol) in 10 mL benzene was added cyclopropylamine (0.78 mL, 11.2 mmol). Purification of the product provided methyl 2-chloro-3-[(cyclopropylamino)sulfonyl]benzoate (355 mg, 54%) as a solid. 1H NMR (400 MHz, $CDCl_3$), δ 8.28 (dd, 1H, $J = 7.9, 1.7$ Hz), 7.90 (dd, 1H, $J = 7.8, 1.7$ Hz), 7.48 (t, 1H, $J = 7.8$ Hz), 5.63 (s, 1H), 3.93 (s, 3H), 2.17 (m, 1H), 0.65-0.58 (m, 2H), 0.57-0.50 (m, 2H); ESI-MS 290 ($M+H$), 312 ($M+Na$). Methyl 2-chloro-3-[(cyclopropylamino)sulfonyl]benzoate was hydrolyzed using aqueous NaOH to provide 2-chloro-3-[(cyclopropylamino)sulfonyl]benzoic acid as a solid, which was used without further purification. ESI-MS 276 ($M+H$), 298 ($M+Na$).

2-chloro-*N*-cyclopropyl-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]benzenesulfonamide (288 mg, 91%) was obtained as a solid from 2-chloro-3-[(cyclopropylamino)sulfonyl]benzoic acid (41 mg, 0.15 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (90 mg, 0.15 mmol) and HATU (62 mg, 0.16 mmol) following the procedure outlined in example 5. 1H NMR (400 MHz, $CDCl_3$), δ 8.18 (m, 1H), 7.65 (m, 1H), 7.56-7.25 (m, 4H), 7.15 (m, 2H), 7.05 (m, 1H), 7.01-6.91 (m, 2H), 5.95-5.44 (m, 2H), 4.61 (m, 1H), 4.23 (m, 1H), 3.45-3.05 (m, 5H), 2.56 (s, 1.5H, rotamer), 2.54 (s, 1.5H, rotamer), 2.43-1.74 (m, 15H), 1.70-1.58 (m, 2H), 0.78 (m, 1H), 0.63-0.50 (m, 2H); ESI-MS 704 ($M+H$).

Example 935

Preparation of 1,1,1-trifluoro-*N*-[3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropyl]methanesulfonamide



Preparation of 2,2-dimethyl-3-[[trifluoromethyl]sulfonyl]amino}propanoic acid.

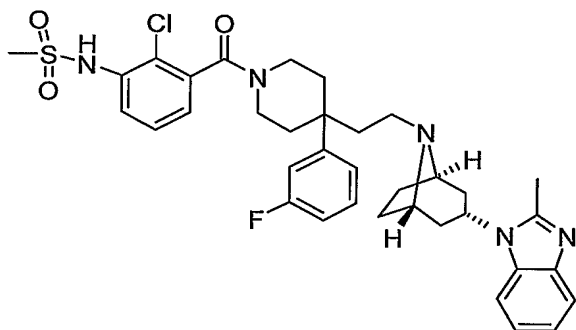
To a -78°C solution of methyl 3-amino-2,2-dimethylpropanoate (318 mg, 2.4 mmol) and Et_3N (0.34 mL, 2.44 mmol) in 4 mL CH_2Cl_2 was added trifluoromethanesulfonic anhydride (0.81 mL, 4.84 mmol). The reaction was stirred for 4h below -40°C and quenched with saturated aqueous NaHCO_3 . The crude methyl 2,2-dimethyl-3-[[trifluoromethyl]sulfonyl]amino}propanoate was isolated and hydrolyzed using aqueous NaOH to provide 2,2-dimethyl-3-[[trifluoromethyl]sulfonyl]amino}propanoic acid which was used without further purification.

1,1,1-trifluoro-*N*-[3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropyl]methanesulfonamide (41 mg, 44%) was obtained as a solid from 2,2-dimethyl-3-[[trifluoromethyl]sulfonyl]amino}propanoic acid (100 mg, 0.40 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^1H NMR (400 MHz, CDCl_3), δ 7.1-7.67 (m, 1H), 7.41-7.21 (m, 4H), 7.07 (m, 1H), 7.02-6.94 (m, 2H), 4.84 (q, 1H, $J = 9.5$ Hz), 3.94 (m, 2H),

3.45 (m, 2H), 3.21 (m, 5H), 2.62 (s, 3H), 2.54 (m, 2H), 2.20 (m, 2H), 2.14-1.95 (m, 6H), 1.87 (m, 2H), 1.81-1.71 (m, 4H), 1.33 (s, 6H); ESI-MS 678 (M+H).

Example 936

Preparation of *N*-{2-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide



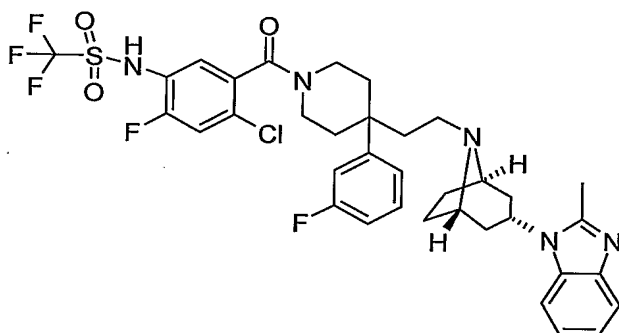
Preparation of 2-chloro-3-[(methylsulfonyl)amino]benzoic acid. To a solution of methyl 3-amino-2-chlorobenzoate (517 mg, 2.79 mmol) and pyridine (0.25 mL, 3.06 mmol) in 8mL CH₂Cl₂ was added methanesulfonylchloride (0.24 mL, 3.06 mmol). After washing with 1M HCl, methyl 2-chloro-3-[(methylsulfonyl)amino]benzoate was isolated as a solid in quantitative yield. ¹H NMR (400 MHz, CDCl₃), δ 7.77 (dd, 1H, J = 8.2, 1.6 Hz), 7.61 (dd, 1H, J = 7.9, 1.6 Hz), 7.33 (t, 1H, J = 7.9 Hz), 7.16 (s, 1H), 3.91 (s, 3H), 2.99 (s, 3H); ESI-MS 262 (M-H). Methyl 2-chloro-3-[(methylsulfonyl)amino]benzoate was hydrolyzed using aqueous NaOH to provide 2-chloro-3-[(methylsulfonyl)amino]benzoic acid as a solid, which was used without further purification. ESI-MS 248 (M-H).

N-{2-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide (18 mg, 20%) was obtained as a solid from 2-chloro-3-[(methylsulfonyl)amino]benzoic acid (49 mg, 0.20 mmol),

1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz, CDCl₃), δ 7.72-7.63 (m, 2H), 7.41-7.25 (m, 4H), 7.16 (m, 2H), 7.07 (m, 1H), 7.02-6.93 (m, 2H), 4.62 (m, 1H), 4.22 (m, 1H), 3.48-3.09 (m, 5H), 3.07 (2, 1.5H, rotamer), 3.04 (s, 1.5H, rotamer), 2.58-2.53 (m, 3H, rotamers), 2.45-2.24 (m, 3H), 2.18-1.61 (m, 15H); ESI-MS 678 (M+H).

Example 937

Preparation of *N*-(4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl]piperidin-1-yl)carbonyl]phenyl)-1,1,1-trifluoromethanesulfonamide



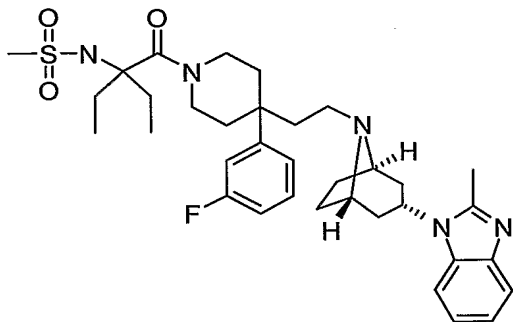
Preparation of 2-chloro-4-fluoro-5-[(trifluoromethyl)sulfonyl]amino}benzoic acid. To a -78 °C solution of methyl 5-amino-2-chloro-4-fluorobenzoate (195 mg, 1.0 mmol) and Et₃N (0.13 mL, 1.0 mmol) in 2 mL CH₂Cl₂ was added trifluoromethanesulfonic anhydride (0.32 mL, 1.9 mmol). The reaction was stirred for 4h below -40 °C and quenched with saturated aqueous NaHCO₃. The crude methyl 2-chloro-4-fluoro-5-[(trifluoromethyl)sulfonyl]amino}benzoate (ESI-MS 336 (M+H)) was isolated and hydrolyzed using aqueous NaOH to provide 2-chloro-4-fluoro-5-[(trifluoromethyl)sulfonyl]amino}benzoic acid (ESI-MS 320 (M-H)) which was used without further purification.

N-{4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide (27 mg, 26%) was obtained as a solid from 2-chloro-4-fluoro-5-[[[(trifluoromethyl)sulfonyl]amino]benzoic acid (90 mg, 0.28 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz, CDCl₃),

□ 7.68 (m, 1H), 7.58-7.46 (m, 1H), 7.38 (m, 1H), 7.31-7.19 (m, 3H), 7.14 (m, 1H), 7.08-6.93 (m, 3H), 5.06 (m, 1H), 4.12 (m, 1H), 3.89-3.63 (m, 2H), 3.48-3.08 (m, 4H), 2.77-2.33 (m, 7H), 2.30-1.76 (m, 12H); ESI-MS 750 (M+H).

Example 938

Preparation of *N*-{1-ethyl-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]propyl}methanesulfonamide



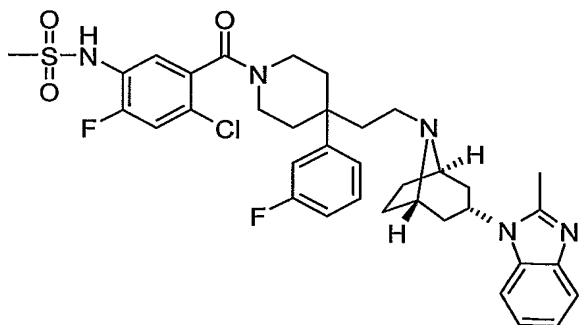
Preparation of 2-ethyl-2-[(methylsulfonyl)amino]butanoic acid. To a solution of 0 °C solution of diethylglycine (205 mg, 1.56 mmol) in 2mL 1M NaOH was added methanesulfonyl chloride (0.14 mL, 1.81 mmol) with periodic stirring and addition of another 2mL 1M NaOH. The reaction mixture was stirred for 1h at 0 °C, 4h at room temperature, and then acidified with 1M HCl and extracted into EtOAc to provide the crude 2-ethyl-2-

[(methylsulfonyl)amino]butanoic acid (37 mg, 11%) as a solid, which was used without further purification. ^1H NMR (400 MHz, CDCl_3), δ 5.19 (s, 1H), 3.06 (s, 3H), 2.14 (m, 2H), 1.92 (m, 2H), 0.96 (t, 6H, $J = 7.4$ Hz).

N-{1-ethyl-1-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]propyl}methanesulfonamide (69 mg, 79%) was obtained as a solid from 2-ethyl-2-[(methylsulfonyl)amino]butanoic acid (37 mg, 0.18 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^1H NMR (400 MHz, CDCl_3), δ 7.65-7.62 (m, 1H), 7.39-7.30 (m, 1H), 7.28 (m, 1H), 7.19-7.11 (m, 2H), 7.06 (m, 1H), 7.01-6.91 (m, 2H), 6.35 (s, 0.3H, rotamer), 6.28 (s, 0.7H, rotamer), 4.75 (br. s, 1H), 4.07-3.96 (m, 2H), 3.39-3.25 (m, 4H), 2.98 (s, 2H, rotamer), 2.97 (s, 1H, rotamer), 2.57 (s, 3H), 2.48-2.38 (m, 2H), 2.31 (m, 2H), 2.24-2.15 (m, 2H), 2.01-1.91 (m, 4H), 1.90-1.74 (m, 8H), 1.74-1.63 (m, 2H), 0.96-0.85 (m, 6H); ESI-MS 638 ($\text{M}+\text{H}$).

Example 939

Preparation of *N*-{4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide



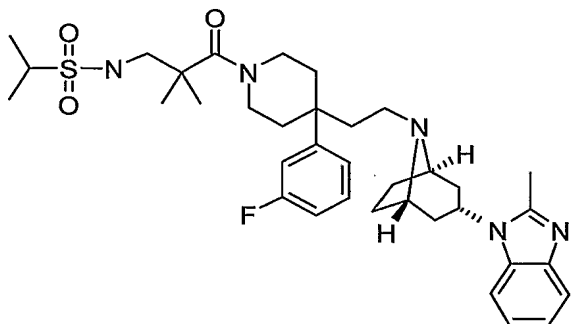
Preparation of 2-chloro-4-fluoro-5-[(methylsulfonyl)amino]benzoic acid. To a solution of methyl 5-amino-2-chloro-4-fluorobenzoate (152 mg, 0.75 mmol) and pyridine (0.07 mL, 0.82 mmol) in 3 mL CH₂Cl₂ was added methanesulfonyl chloride (0.06 mL, 0.82 mmol). After 3 days at room temperature, the reaction mixture was washed with saturated aqueous NaHCO₃ and filtered through a silica plug to provide methyl 2-chloro-4-fluoro-5-[(methylsulfonyl)amino]benzoate (96 mg, 44%) as a solid (ESI-MS 280 (M-H)), which was hydrolyzed using aqueous NaOH to provide 2-chloro-4-fluoro-5-[(methylsulfonyl)amino]benzoic acid (ESI-MS 266 (M-H)), which was used without further purification.

N-{4-chloro-2-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide (15.9 mg, 7%) was obtained as a solid from 2-chloro-4-fluoro-5-[(methylsulfonyl)amino]benzoic acid (91 mg, 0.34 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (210 mg, 0.34 mmol) and HATU (194 mg, 0.51 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz, CDCl₃), δ 7.66 (m, 1H), 7.55 (m, 0.5H, rotamer), 7.42-7.32 (m, 1.5H, rotamer), 7.31-7.27 (m, 1H), 7.25-7.11 (m, 3H), 7.07 (m, 1H), 7.02-6.93 (m, 2H), 4.65 (br. s, 1H), 4.29-4.11 (m, 1H), 3.47-3.11 (m, 5H), 3.08 (s, 1.5H, rotamer), 3.05 (s, 1.5H, rotamer), 2.56 (s, 3H), 2.46-2.35 (m, 2H), 2.33-2.24 (m, 1H), 2.18-2.10 (m, 1H), 2.00-1.73 (m, 10H), 1.67 (m, 2H); ESI-MS 696 (M+H).

Example 940

Preparation of *N*-[3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropyl]propane-2-sulfonamide

675

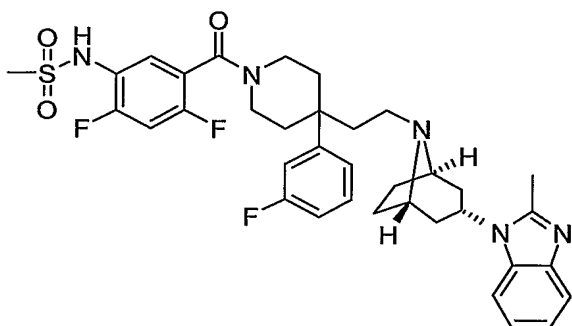


Preparation of 3-[(isopropylsulfonyl)amino]-2,2-dimethylpropanoic acid. To a solution of methyl 3-amino-2,2-dimethylpropanoate (200 mg, 1.53 mmol) and Et₃N (0.64 mL, 4.59 mmol) in 2 mL CH₂Cl₂ was added isopropylsulfonyl chloride (0.34 mL, 3.05 mmol). The reaction was stirred for 24h, quenched by the addition of saturated aqueous NaHCO₃, extracted with CHCl₃, and chromatographed (1:1 hex:EtOAc) to provide methyl 3-[(isopropylsulfonyl)amino]-2,2-dimethylpropanoate (77 mg, 21%) as a solid. ¹H NMR (400 MHz, CDCl₃), 4.78 (t, 1H, J = 6.6 Hz), 3.68 (s, 3H), 3.20-3.11 (m, 3H), 1.36 (d, 6H, J = 6.9 Hz), 1.23 (s, 6H). Methyl 3-[(isopropylsulfonyl)amino]-2,2-dimethylpropanoate was hydrolyzed using aqueous NaOH to provide 3-[(isopropylsulfonyl)amino]-2,2-dimethylpropanoic acid, which was used without further purification.

N-[3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropyl]propane-2-sulfonamide (130mg, 74%) was obtained as a solid from 3-[(isopropylsulfonyl)amino]-2,2-dimethylpropanoic acid (60 mg, 0.27 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (164 mg, 0.27 mmol) and HATU (154 mg, 0.41 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz, CDCl₃), δ 7.68-7.64 (m, 1H), 7.36 (m, 1H), 7.29 (m, 1H), 7.16 (m, 2H), 7.08 (m, 1H), 7.00 (m, 1H), 6.96 (m, 1H), 5.36 (t, 1H, J = 6.6 Hz), 4.65 (br. s, 1H), 3.93 (m, 2H), 3.33-3.20 (m, 4H), 3.15 (m, 1H), 3.10 (m, 2H), 2.58 (s, 3H), 2.40 (m, 2H), 2.19 (m, 2H), 2.00-1.73 (m, 10H), 1.67 (m, 2H), 1.39 (s, 3H), 1.37 (s, 3H), 1.33 (s, 6H); ESI-MS 652 (M+H).

Example 941

Preparation of *N*-{2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide



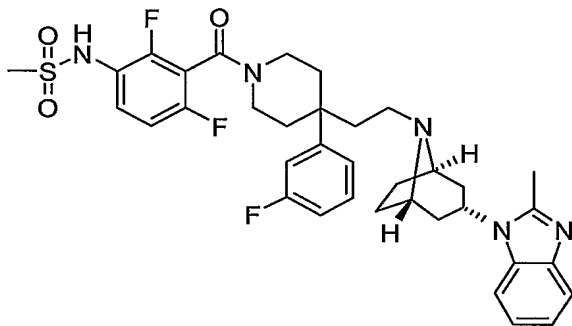
Preparation of 2,4-difluoro-5-[(methanesulfonyl)amino]benzoic acid. To a solution of methyl 5-amino-2,4-difluorobenzoate (252 mg, 1.35 mmol) and pyridine (0.13 mL, 1.61 mmol) in 5 mL CH₂Cl₂ was added methanesulfonyl chloride (0.12 mL, 1.48 mmol). After 24h at room temperature, the reaction mixture was washed with saturated aqueous NaHCO₃ and extracted with CHCl₃ to provide crude methyl 2, 4-difluoro-5-[(methanesulfonyl)amino]benzoate as a solid (ESI-MS 264 (M-H)), which was hydrolyzed using aqueous NaOH to provide 2,4-difluoro-5-[(methanesulfonyl)amino]benzoic acid (ESI-MS 250 (M-H)), which was used without further purification.

N-{2,4-difluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide (7.0 mg, 13%) was obtained as a solid from 2,4-difluoro-5-[(methanesulfonyl)amino]benzoic acid (20 mg, 0.08 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (48 mg, 0.08 mmol) and HATU (45 mg, 0.12 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz, CDCl₃), δ 7.73-7.68 (m, 1H), 7.60 (s, 1H), 7.41 (m, 1H), 7.25-7.15 (m, 3H), 7.12-7.07 (m, 1H), 7.04-6.93 (m, 3H), 4.26-4.11 (m, 1H), 3.89-3.63 (m, 2H), 3.58-3.43 (m, 2H), 3.29-3.16 (m, 2H), 3.07

(s, 2H, rotamer), 3.02 (s, 1H, rotamer), 2.70 (s, 3H), 2.41-1.61 (m, 16H); ESI-MS 681 (M+H).

Example 942

Preparation of *N*-{2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide



Preparation of 2,6-difluoro-3-[(methylsulfonyl)amino]benzoic acid. To a solution of methyl 3-amino-2,6-difluorobenzoate (530 mg, 2.83 mmol) and pyridine (0.28 mL, 3.40 mmol) in 10 mL CH₂Cl₂ was added methanesulfonyl chloride (0.24 mL, 3.11 mmol). After 24h at room temperature, the reaction mixture was washed with saturated aqueous NaHCO₃ and extracted with CHCl₃ to provide crude methyl 2,6-difluoro-3-[(methylsulfonyl)amino]benzoate as a solid (ESI-MS 264 (M-H)), which was hydrolyzed using aqueous NaOH to provide 2,6-difluoro-3-[(methylsulfonyl)amino]benzoic acid (ESI-MS 250 (M-H)), which was used without further purification.

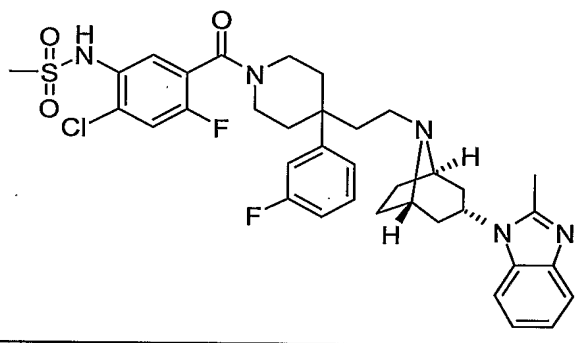
N-{2,4-difluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide (30.5 mg, 49%) was obtained as a solid from 2,6-difluoro-3-[(methylsulfonyl)amino]benzoic acid (26 mg, 0.10 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-

yl)-2-methyl-1*H*-benzimidazole dihydrochloride (56 mg, 0.09 mmol) and HATU (53 mg, 0.14 mmol) following the procedure outlined in example 5.

¹H NMR (400 MHz, CDCl₃), δ 7.79 (m, 1H), 7.55 (m, 1H), 7.42 (m, 1H), 7.34-7.23 (m, 3H), 7.13 (m, 1H), 7.05-6.94 (m, 3H), 6.02 (br. s, 1H), 4.13 (m, 1H), 3.98-3.80 (m, 2H), 3.59-3.43 (m, 2H), 3.23 (m, 1H), 3.08 (s, 3H), 2.97-3.85 (m, 2H), 2.82 (s, 3H), 2.61-2.46 (m, 2H), 2.39-1.86 (m, 12H); ESI-MS 681 (M+H).

Example 943

Preparation of *N*-{2-chloro-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl]piperidin-1-yl)carbonyl]phenyl}methanesulfonamide

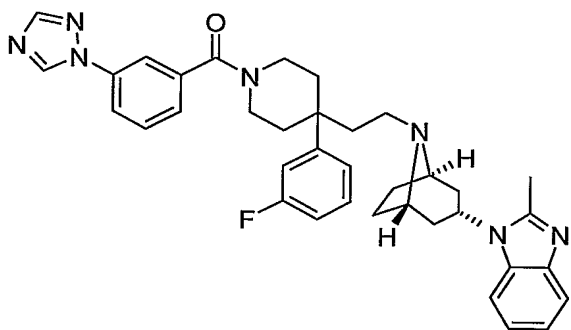


Preparation of 4-chloro-2-fluoro-5-[(methanesulfonyl)amino]benzoic acid. To a solution of methyl 5-amino-4-chloro-2-fluorobenzoate (248 mg, 1.22 mmol) and pyridine (0.12 mL, 1.46 mmol) in 5 mL CH₂Cl₂ was added methanesulfonyl chloride (0.10 mL, 1.34 mmol). After 5 days at room temperature, the reaction mixture was washed with saturated aqueous NaHCO₃ and extracted with CHCl₃ to provide crude methyl 4-chloro-2-fluoro-5-[(methanesulfonyl)amino]benzoate as a solid (ESI-MS 280 (M-H)), which was hydrolyzed using aqueous NaOH to provide 4-chloro-2-fluoro-5-[(methanesulfonyl)amino]benzoic acid (ESI-MS 266 (M-H)), which was used without further purification.

N-{2-chloro-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide (56 mg, 59%) was obtained as a solid from 4-chloro-2-fluoro-5-[(methylsulfonyl)amino]benzoic acid (43 mg, 0.16 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.13 mmol) and HATU (78 mg, 0.20 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz, CDCl₃), δ 7.68-7.61 (m, 1H), 7.61 (br. s, 1H), 7.36 (m, 1H), 7.31-7.26 (m, 1H), 7.25-7.21 (m, 1H), 7.21-7.12 (m, 2H), 7.07 (m, 1H), 7.02-6.93 (m, 2H), 4.68 (br. s, 1H), 4.19 (m, 1H), 3.50-3.15 (m, 5H), 3.04 (s, 3H), 2.58 (s, 3H), 2.51-2.34 (m, 2H), 2.28 (m, 2H), 2.15 (m, 2H), 2.07-1.76 (m, 10H), 1.69 (m, 2H); ESI-MS 696 (M+H).

Example 944

Preparation of 1-[(1*R*,5*S*)-8-(2-{4-(3-fluorophenyl)-1-[3-(1*H*-1,2,4-triazol-1-yl)benzoyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole

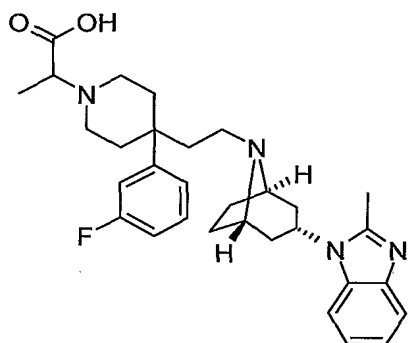


1-[(1*R*,5*S*)-8-(2-{4-(3-fluorophenyl)-1-[3-(1*H*-1,2,4-triazol-1-yl)benzoyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole (89 mg, 47%) was obtained as a solid from 3-(1*H*-1,2,4-triazol-1-yl)benzoic acid (107 mg, 0.56 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (160 mg, 0.31 mmol) and HATU (176 mg, 0.46 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz,

CDCl₃), δ 8.58 (s, 1H), 8.11 (s, 1H), 7.77-7.72 (m, 2H), 7.67 (d, 1H, J = 7.9 Hz), 7.56 (t, 1H, J = 7.8 Hz), 7.43-7.24 (m, 3H), 7.17 (m, 2H), 7.09 (d, 1H, J = 7.7 Hz), 7.04-6.94 (m, 2H), 4.61 (m, 1H), 4.19 (m, 1H), 3.60 (m, 1H), 3.47-3.17 (m, 3H), 2.56 (s, 3H), 2.43-2.26 (m, 3H), 2.13 (m, 1H), 2.02-1.55 (m, 12H); ESI-MS 618 (M+H).

Example 945

Preparation of 2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)propanoic acid



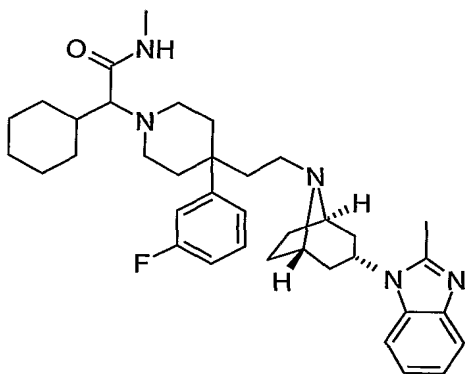
To a -78°C solution of benzyl 2-hydroxypropanoate (250 mg, 1.39 mmol) and 4A molecular sieves in 2 mL CH₂Cl₂ was added trifluoromethanesulfonic anhydride (0.33 mL, 1.97 mmol). After stirring for 10 min at this temperature, 2,6-lutidine (0.31 mL, 2.62 mmol) was added. After 15 min, diisopropylethylamine (0.46 mL, 2.62 mmol) was added and after another 15 min, a solution of 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (400 mg, 0.66 mmol) in 3 mL CH₂Cl₂ was added. The reaction mixture was stirred at -78°C , then allowed to warm to room temperature overnight, washed with saturated aqueous NaHCO₃, and purified by chromatography (3% (2M NH₃ / MeOH) in CHCl₃) to provide benzyl 2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)propanoate (146 mg, 37%) as a solid. ¹H NMR (400 MHz, CDCl₃), δ 7.68

(m, 1H), 7.37-7.26 (m, 7H), 7.22-7.13 (m, 2H), 7.08 (m, 1H), 6.98 (m, 1H), 6.92 (m, 1H), 5.09 (s, 2H), 4.62 (m, 1H), 3.39-3.17 (m, 2H), 2.89-1.26 (m, 27H); ESI-MS 609 (M+H).

A solution of benzyl 2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)propanoate (136 mg, 0.223 mmol) in 8mL MeOH was stirred for 3h under an atmospheric pressure of hydrogen and in the presence of catalytic 5% Pd/C. Filtration and evaporation afforded 2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)propanoic acid (90.0 mg, 78%) as a solid. ¹H NMR (400 MHz, CDCl₃), δ 7.69 (m, 1H), 7.40 (m, 1H), 7.26-7.12 (m, 4H), 7.09-6.95 (m, 2H), 5.37 (m, 1H), 3.85-3.55 (m, 5H), 2.81-1.77 (18H), 2.62 (s, 3H), 1.61-1.41 (3H); ESI-MS 517 (M-H).

Example 946

Preparation of 2-cyclohexyl-2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-*N*-methylacetamide



Preparation of cyclohexyl(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetic acid.

To a -78 °C solution of benzyl cyclohexyl(hydroxy)acetate (61 mg, 0.25 mmol) and 4A molecular sieves in 1.2 mL CH₂Cl₂ was added

trifluoromethanesulfonic anhydride (0.05 mL, 0.30 mmol). After stirring for 10 min at this temperature, 2,6-lutidine (0.06 mL, 0.49 mmol) was added. After 15 min, diisopropylethylamine (0.09 mL, 0.49 mmol) was added and after another 15 min, a solution of 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (153 mg, 0.30 mmol) in 1 mL CH₂Cl₂ was added. The reaction mixture was stirred at -78 °C, then allowed to warm to room temperature overnight, washed with saturated aqueous NaHCO₃, and purified by preparatory TLC using 5% MeOH in CHCl₃ to afford benzyl cyclohexyl(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetate (33 mg, 20%) as an oil. ¹H NMR (400 MHz, CDCl₃), δ 7.68 – 7.64 (m, 1H), 7.33-7.23 (m, 7H), 7.20-7.12 (m, 2H), 7.05 (m, 1H), 6.97 (m, 1H), 6.89 (m, 1H), 5.05 (AB_q, 2H, *J* = 12.3 Hz), 4.61 (m, 1H), 3.26-3.18 (m, 2H), 2.92 (d, 1H, *J* = 10.4 Hz), 2.70 (m, 1H), 2.64-2.50 (m, 2H), 2.57 (s, 3H), 2.46-2.30 (m, 3H), 2.12-0.81 (m, 25H); ESI-MS 677 (M+H).

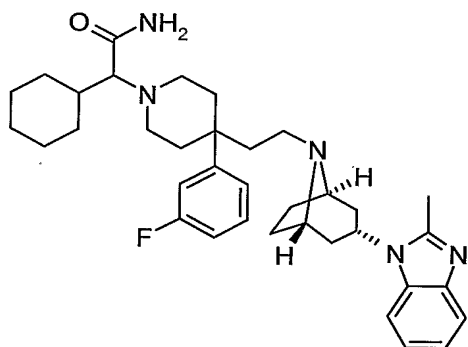
A solution of benzyl cyclohexyl(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetate (23.8 mg, 0.035 mmol) in 3mL MeOH was stirred for 3h under an atmospheric pressure of hydrogen and in the presence of catalytic 5% Pd/C. Filtration and evaporation afforded cyclohexyl(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetic acid (17.5 mg, 85%). ESI-MS 585 (M-H).

To a solution of cyclohexyl(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetic acid (22.0 mg, 0.037 mmol), methylamine (0.056 mL of a 2M solution in THF, 0.11 mmol), N-hydroxybenzotriazole (10.1 mg, 0.075 mmol) and N-methylmorpholine (0.10 mL, 0.094 mmol) in 1 mL DMF was added EDC (14 mg, 0.075 mmol). The reaction mixture was stirred for 24h, then diluted with 4:1 EtOAc:hex and washed with saturated aqueous NaHCO₃, dried (Na₂SO₄)

and chromatographed (5% (2M NH₃ / MeOH) in CHCl₃) to provide 2-cyclohexyl-2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-*N*-methylacetamide (8.1 mg, 36%) as a solid. ¹H NMR (400 MHz, CDCl₃), δ 7.66 (m, 1H), 7.33-7.27 (m, 2H), 7.20-7.11 (m, 2H), 7.05 (m, 1H), 6.98 (m, 1H), 6.90 (m, 1H), 4.64 (m, 1H), 3.33-3.20 (m, 2H), 2.80 (d, 3H, *J* = 4.9 Hz), 2.59 (s, 3H), 2.47-0.79 (m, 27H); ESI-MS 600 (M+H).

Example 947

Preparation of 2-cyclohexyl-2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetamide

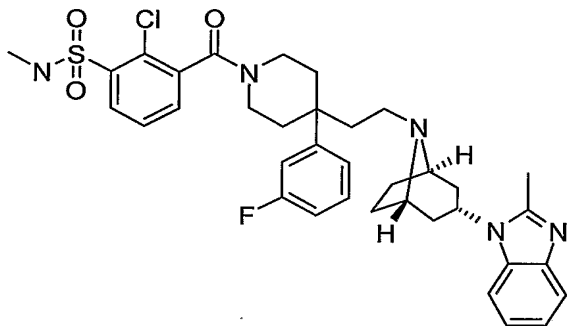


To a solution of cyclohexyl(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetic acid (22.0 mg, 0.037 mmol), hydroxylamine (0.2 mL of a 28% solution in water, 3.3 mmol), *N*-hydroxybenzotriazole (10.1 mg, 0.075 mmol) and *N*-methylmorpholine (0.10 mL, 0.094 mmol) in 1 mL DMF was added EDC (14 mg, 0.075 mmol). The reaction mixture was stirred for 24h, then diluted with 4:1 EtOAc:hex and washed with saturated aqueous NaHCO₃, dried (Na₂SO₄) and chromatographed (5% (2M NH₃ / MeOH) in CHCl₃) to provide 2-cyclohexyl-2-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)acetamide

(7.7 mg, 35%) as a solid. ^1H NMR (400 MHz, CDCl_3), δ 7.66 (m, 1H), 7.34-7.27 (m, 2H), 7.20-7.12 (m, 2H), 7.06 (m, 1H), 6.99 (m, 1H), 6.90 (m, 1H), 4.61 (m, 1H), 3.27-3.19 (m, 2H), 2.73-2.62 (m, 2H), 2.58 (s, 3H), 2.47-0.78 (m, 27H); ESI-MS 589 (M+H)

Example 948

Preparation of 2-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methylbenzenesulfonamide



Preparation of 2-chloro-3-[(methylamino)sulfonyl]benzoic acid. To a solution of

To a solution of methyl 2-chloro-3-(chlorosulfonyl)benzoate (608 mg, 2.26 mmol) and K_2CO_3 (770 mg, 5.6 mmol) in 10 mL benzene was added a 2M solution of methylamine in THF (5.6 mL, 11.2 mmol). Purification of the product (2:1 hex:EtOAc) provided methyl 2-chloro-3-

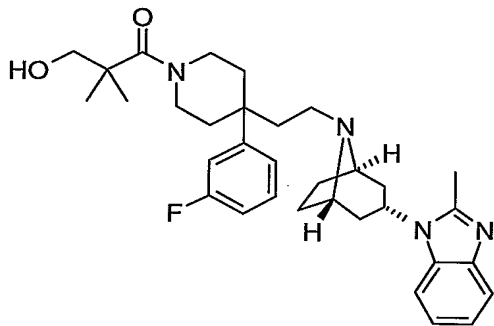
[(methylamino)sulfonyl]benzoate (430 mg, 72%) as a solid. ^1H NMR (400 MHz, CDCl_3), δ 8.23 (dd, 1H, $J = 7.9, 1.7$ Hz), 7.90 (dd, 1H, $J = 7.8, 1.7$ Hz), 7.48 (t, 1H, $J = 7.9$ Hz), 5.16 (q, 1H, $J = 5.2$ Hz), 3.94 (s, 3H), 2.62 (d, 3H, $J = 5.3$ Hz); ESI-MS 264 (M+H). Methyl 2-chloro-3-

[(methylamino)sulfonyl]benzoate was hydrolyzed using aqueous NaOH to provide 2-chloro-3-[(methylamino)sulfonyl]benzoic acid as a solid, which was used without further purification. ESI-MS 250 (M+H), 272 (M+Na).

2-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-*N*-methylbenzenesulfonamide (87 mg, 62%) was obtained as a solid from 2-chloro-3-[(methylamino)sulfonyl]benzoic acid (52 mg, 0.21 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (127 mg, 0.21 mmol) and HATU (87 mg, 0.23 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz, CDCl₃), δ 8.40 (m, 1H), 7.62 (m, 1H), 7.53-7.28 (m, 4H), 7.13 (m, 2H), 7.04 (m, 1H), 6.99-6.90 (m, 2H), 5.92-5.59 (m, 2H), 4.60 (m, 1H), 4.2 (m, 1H), 3.42-3.03 (m, 6H), 2.63-2.58 (m, 3H, rotamers), 2.54 (s, 1.5H, rotamer), 2.52 (s, 1.5H, rotamer), 2.41-2.23 (m, 3H), 2.17-1.58 (m, 11H); ESI-MS 678 (M+H).

Example 949

Preparation of 3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropan-1-ol

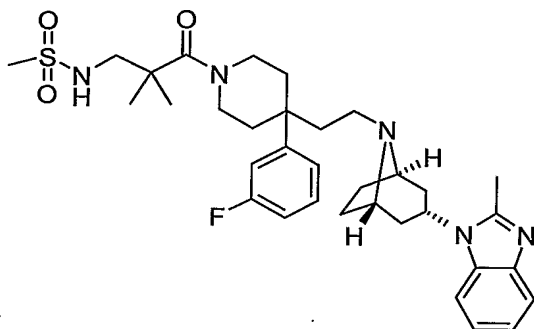


3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropan-1-ol (63 mg, 88%) was obtained as a solid from 3-hydroxy-2,2-dimethylpropanoic acid (23 mg, 0.20 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (80 mg, 0.13 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz, CDCl₃), δ 7.67-7.63

(m, 1H), 7.38-7.28 (m, 2H), 7.15 (m, 2H), 7.08 (m, 1H), 7.02-6.92 (m, 2H), 4.60 (m, 1H), 3.90 (m, 2H), 3.72 (m, 1H), 3.45 (m, 2H), 3.25 (m, 4H), 2.57 (s, 3H), 2.37 (m, 2H), 2.19 (m, 2H), 1.99-1.85 (m, 6H), 1.85-1.74 (m, 4H), 1.63 (m, 2H), 1.26 (s, 6H); ESI-MS 547 (M+H).

Example 950

Preparation of *N*-[3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropyl]methanesulfonamide

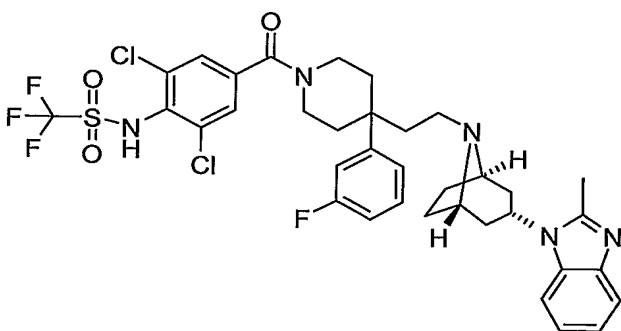


Preparation of 2,2-dimethyl-3-[(methylsulfonyl)amino]propanoic acid. To a solution of methyl 3-amino-2,2-dimethylpropanoate (249 mg, 1.90 mmol) and Et₃N (0.80 mL, 5.70 mmol) in 2 mL CH₂Cl₂ was added methanesulfonyl chloride (0.29 mL, 3.80 mmol). The reaction was stirred for 2 days, quenched by the addition of saturated aqueous NaHCO₃, extracted with CHCl₃, and chromatographed (1:1 hex:EtOAc) to provide methyl 2,2-dimethyl-3-[(methylsulfonyl)amino]propanoate (124 mg, 31%) as a clear oil. ¹H NMR (400 MHz, CDCl₃), 4.95 (t, 1H, J = 6.8 Hz), 3.69 (s, 3H), 3.16 (d, 2H, J = 6.8 Hz), 2.95 (s, 3H), 1.24 (s, 6H). Methyl 2,2-dimethyl-3-[(methylsulfonyl)amino]propanoate was hydrolyzed using aqueous NaOH to provide 2,2-dimethyl-3-[(methylsulfonyl)amino]propanoic acid, which was used without further purification. ¹H NMR (400 MHz, CDCl₃), □ 10.28 (br. s, 1H), 5.56 (br. s, 1H), 3.14 (s, 2H), 2.94 (s, 3H), 1.25 (s, 6H).

N-[3-(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropyl]methanesulfonamide (41 mg, 48%) was obtained as a solid from 2,2-dimethyl-3-[(methylsulfonyl)amino]propanoic acid (38 mg, 0.20 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz, CDCl₃), δ 7.63 (m, 1H), 7.34 (m, 1H), 7.28 (m, 1H), 7.14 (m, 2H), 7.06 (m, 1H), 6.99 (m, 1H), 6.94 (m, 1H), 5.52 (t, 1H, *J* = 6.8 Hz), 4.63 (m, 1H), 3.89 (m, 2H), 3.24 (m, 4H), 3.08 (d, 2H, *J* = 6.8 Hz), 2.93 (s, 3H), 2.56 (s, 3H), 2.37 (m, 2H), 2.18 (m, 2H), 1.92 (m, 6H), 1.78 (m, 4H), 1.64 (m, 2H), 1.32 (s, 6H); ESI-MS 624 (M+H).

Example 951

Preparation of *N*-{2,6-dichloro-4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide

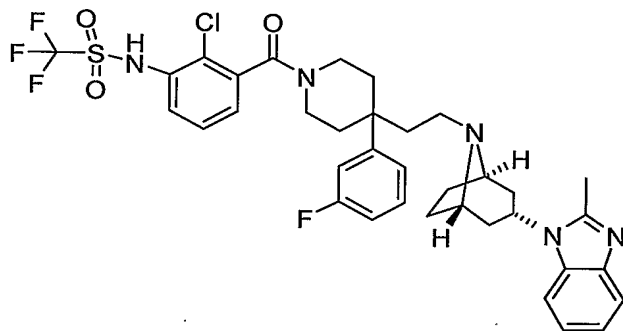


N-{2,6-dichloro-4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide (63 mg, 60%) was obtained as an oil from 3,5-dichloro-4-[[[(trifluoromethyl)sulfonyl]amino]benzoic acid (70 mg, 0.21 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole

dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^1H NMR (400 MHz, CDCl_3), δ 7.68-7.64 (m, 1H), 7.37-7.25 (m, 4H), 7.18 (m, 2H), 7.08 (m, 1H), 7.01-6.90 (m, 2H), 5.17 (m, 1H), 4.02 (m, 1H), 3.52 (m, 1H), 3.30 (m, 2H), 2.64 (s, 3H), 2.56 (m, 2H), 2.23-1.69 (m, 13H); ESI-MS 766 (M+H).

Example 952

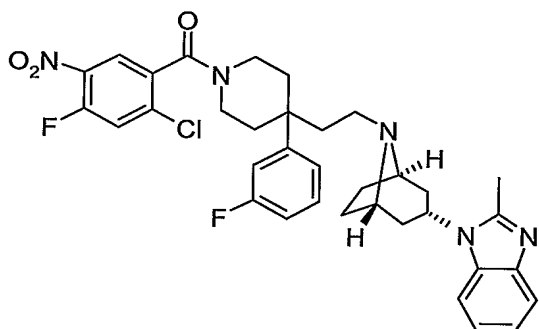
Preparation of *N*-{2-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide



N-{2-chloro-3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide (12 mg, 12%) was obtained as a solid from 2-chloro-3-[[[(trifluoromethyl)sulfonyl]amino]benzoic acid (66 mg, 0.22 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ^1H NMR (400 MHz, CDCl_3), δ 7.70-7.64 (m, 1H), 7.58 (m, 1H), 7.42-7.28 (m, 2H), 7.25-6.92 (m, 5H), 6.88-6.74 (m, 2H), 5.00-4.70 (m, 1H), 4.32-4.00 (m, 1H), 3.75-3.00 (m, 5H), 2.58 (s, 3H), 2.32-1.20 (m, 17H); ESI-MS 732 (M+H).

Example 953

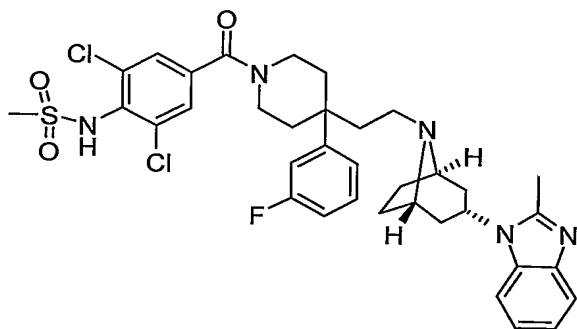
Preparation of 1-((1*R*,5*S*)-8-{2-[1-(2-chloro-4-fluoro-5-nitrobenzoyl)-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole



1-((1*R*,5*S*)-8-{2-[1-(2-chloro-4-fluoro-5-nitrobenzoyl)-4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (14 mg, 16%) was obtained as an oil from 2-chloro-4-fluoro-5-nitrobenzoic acid (39 mg, 0.18 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz, CDCl₃), δ 7.66 (m, 1H), 7.43-7.27 (m, 3H), 7.16 (m, 2H), 7.07 (m, 1H), 7.03-6.93 (m, 3H), 4.62 (m, 1H), 4.24 (m, 1H), 3.46-3.07 (m, 6H), 2.57 (s, 3H), 2.44-1.59 (m, 15H); ESI-MS 648 (M+H).

Example 954

Preparation of *N*-{2,6-dichloro-4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide

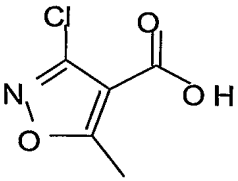
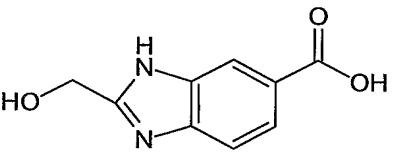
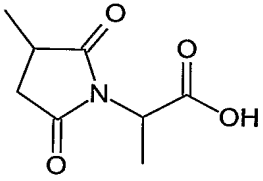
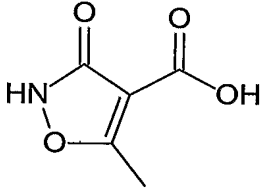
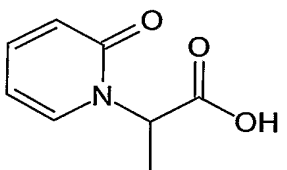
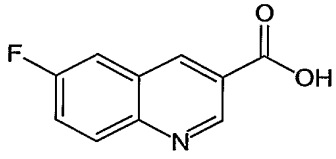
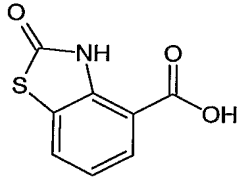


N-{2,6-dichloro-4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}methanesulfonamide (28 mg, 28%) was obtained as a solid from 3,5-dichloro-4-[(methylsulfonyl)amino]benzoic acid (59 mg, 0.21 mmol), 1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (83 mg, 0.14 mmol) and HATU (75 mg, 0.20 mmol) following the procedure outlined in example 5. ¹H NMR (400 MHz, CDCl₃), δ 7.62 (m, 1H), 7.37-7.22 (m, 3H), 7.13 (m, 2H), 7.05 (m, 1H), 7.01-6.88 (m, 3H), 4.58 (m, 1H), 4.12 (m, 1H), 3.55-3.22 (m, 5H), 3.21 (m, 3H, rotamers), 2.53 (m, 3H, rotamers), 2.41-1.56 (m, 15H); ESI-MS 712 (M+H).

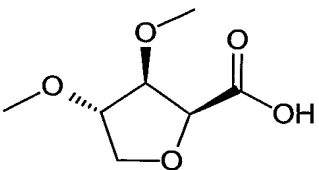
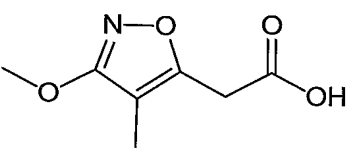
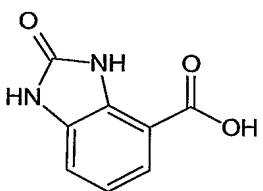
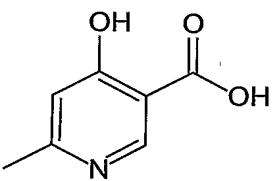
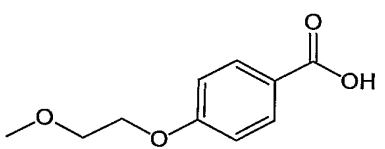
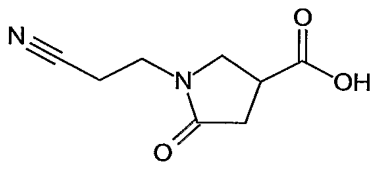
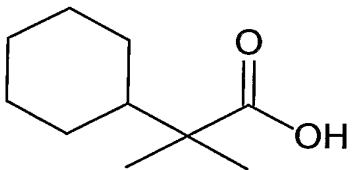
Additional examples of a the formula below were generated by coupling acids listed in the table using method A in example 5.

Example	% Yield	Acid	Method used	Observed mass (M+1)
958			A	556

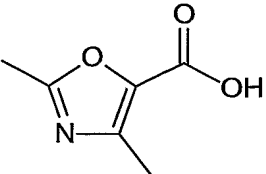
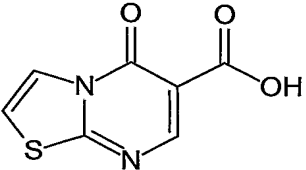
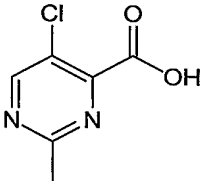
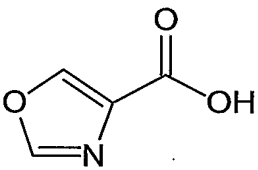
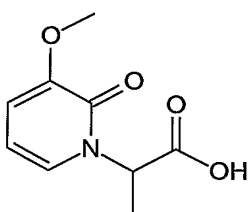
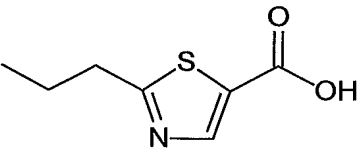
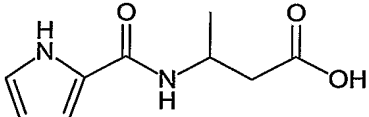
691

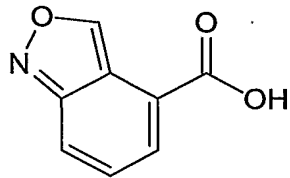
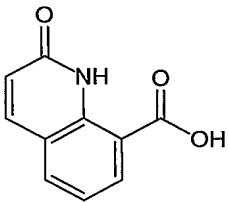
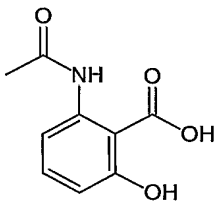
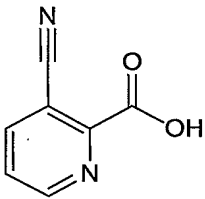
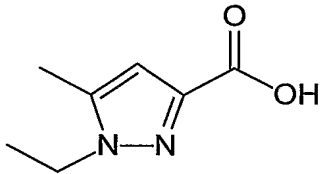
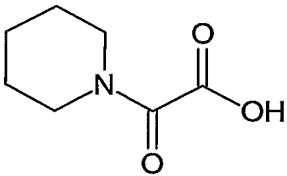
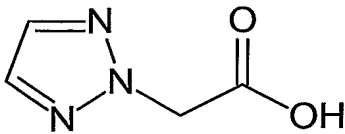
959	47	 <chem>CC1=C(C(=O)O)C(=C(C1)N=O)Cl</chem>	A	572
960	53	 <chem>OCc1c[nH]c2ccc(cc2n1)C(=O)O</chem>	A	603
961	45	 <chem>CC1(C)CC(=O)N(C1C(=O)O)C(C)C</chem>	A	596
962	28	 <chem>CC1=C(C(=O)O)C(=O)NC1=O</chem>	A	554
963	57	 <chem>CC(C)(C(=O)O)N1C=CC=CC1=O</chem>	A	578
964	59	 <chem>Fc1ccc2nc(ccc2c1)C(=O)O</chem>	A	602
965	30	 <chem>CC(C)(C(=O)O)S1C(=O)NC1c2ccccc2</chem>	A	606

692

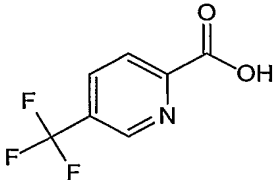
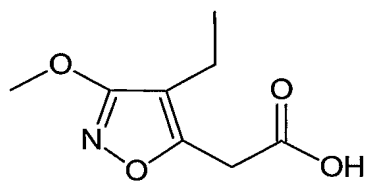
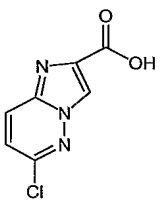
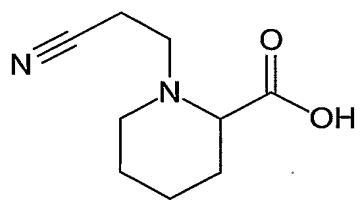
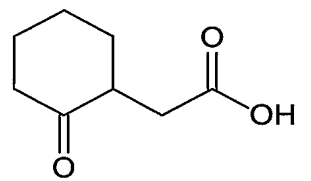
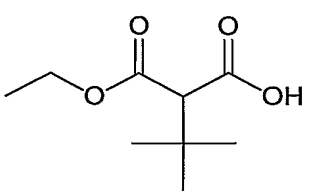
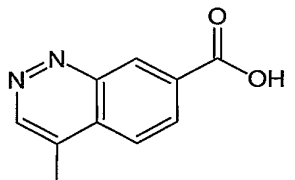
966	46	 <chem>COC[C@H]1O[C@@H](C(=O)O)[C@H](OC)[C@@H]1O</chem>	A	587
967	57	 <chem>COc1cc(C)nn1CC(=O)O</chem>	A	582
968	40	 <chem>O=C1NC2=CC=C(C(=O)O)C=C2N1</chem>	A	589
969	43	 <chem>CC1=CC=C(C(=O)O)N=C1O</chem>	A	564
970	40	 <chem>COCCOC1=CC=C(C(=O)O)C=C1</chem>	A	607
971	44	 <chem>N#CCCC1CC(=O)N1C(=O)O</chem>	A	593
972	54	 <chem>CC(C)(C1CCCCC1)C(=O)O</chem>	A	581

693

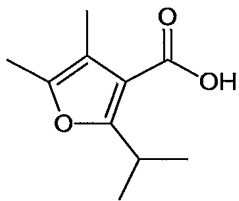
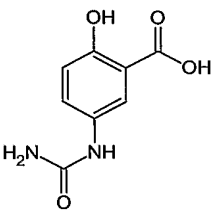
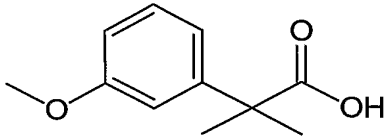
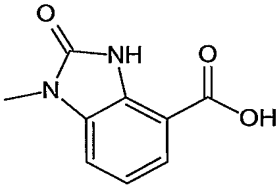
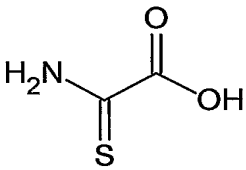
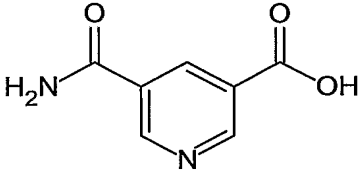
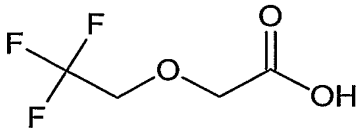
973	54	 <chem>CC1=CN(C)C(=O)O1</chem>	A	552
974	42	 <chem>O=C1C=CN2C(=O)N(C2)C1C(=O)O</chem>	A	607
975	48	 <chem>CC1=NC(=C(N=C1Cl)C(=O)O</chem>	A	583
976	28	 <chem>C1=CN(C=C1)C(=O)O</chem>	A	524
977	54	 <chem>COc1cc(C)nc(C(=O)O)c1=O</chem>	A	608
978	45	 <chem>CCC1=NC=C(S1)C(=O)O</chem>	A	582
979	51	 <chem>CC(C)C(=O)c1ccc[nH]1C(=O)O</chem>	A	607

980	47		A	574
981	31		A	600
982	31		A	606
983	16		A	559
984	38		A	565
985	42		A	568
986	21		A	538

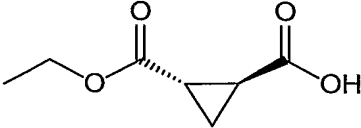
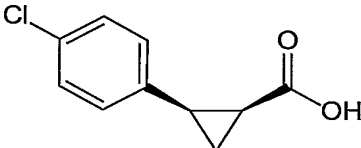
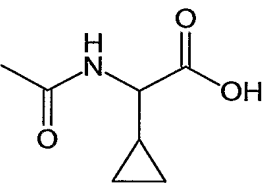
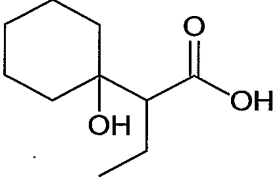
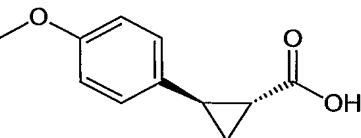
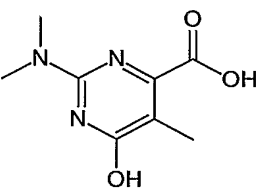
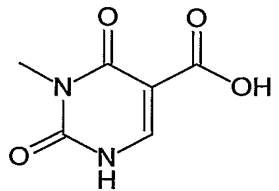
695

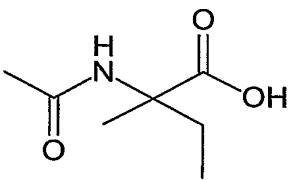
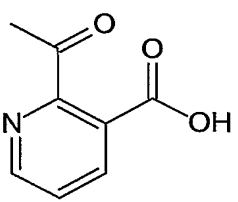
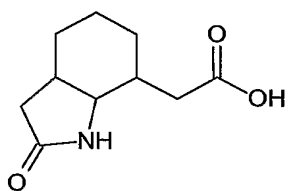
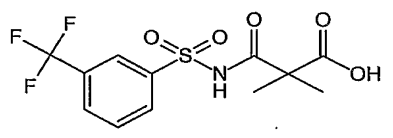
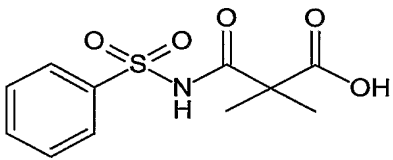
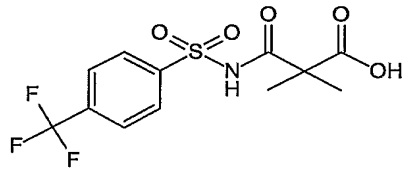
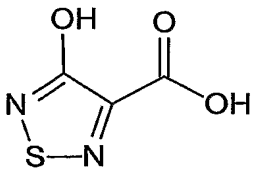
987	34		A	602
988	40		A	596
989	20		A	608
990	55		A	593
991	46		A	567
992	49		A	599
993	32		A	599

696

994	45		A	593
995	16		A	607
996	44		A	605
997	40		A	603
998	20		A	516
999	34		A	577
1000	33		A	569

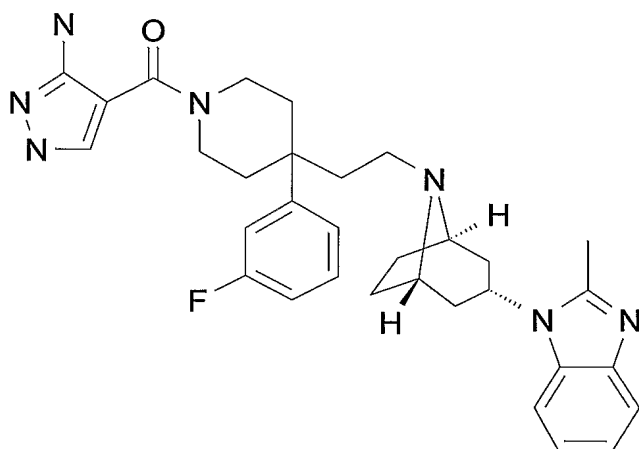
697

1001	29	 <chem>CCOC(=O)[C@H]1CC1C(=O)O</chem>	A	569
1002	45	 <chem>Clc1ccc(cc1)[C@H]2CC2C(=O)O</chem>	A	607
1003	43	 <chem>CC(=O)N[C@H]1CC1C(=O)O</chem>	A	568
1004	45	 <chem>CC(O)[C@H]1CCCCC1C(=O)O</chem>	A	597
1005	42	 <chem>COc1ccc(cc1)[C@H]2CC2C(=O)O</chem>	A	603
1006	16	 <chem>CN1C=NC2=C(N1)C(=O)O[C@H]2C(=O)O</chem>	A	608
1007	18	 <chem>CN1C=NC2=C(N1)C(=O)O[C@H]2C(=O)O</chem>	A	581

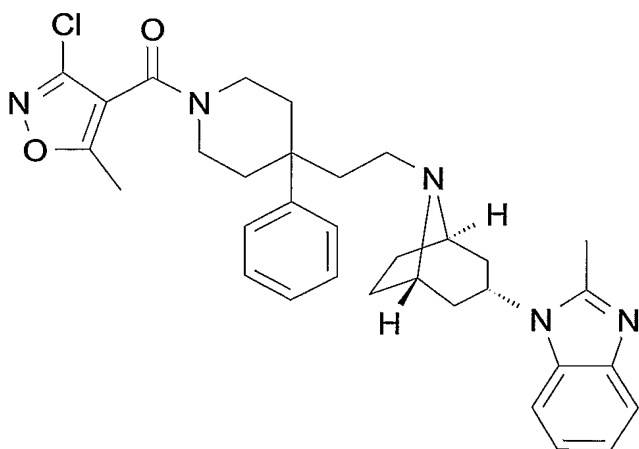
1008	21		A	570
1009	34		A	576
1010	43		A	608
1011			A	768
1012			A	700
1013			A	768
1014			A	575

Example 958

4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-1H-pyrazol-3-amine

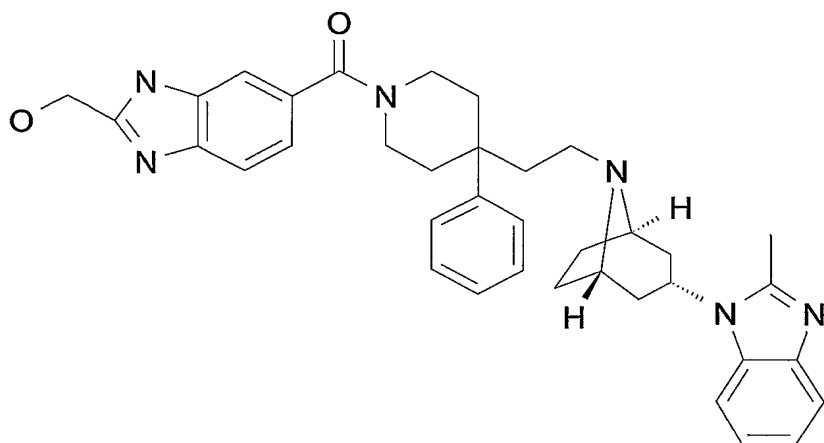
Example 959

1-[(1R,5S)-8-(2-{1-[(3-chloro-5-methylisoxazol-4-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

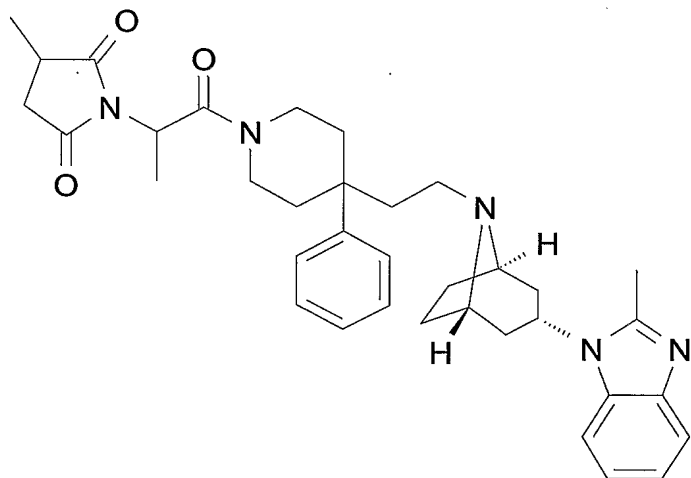
Example 960

{6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1H-benzimidazol-2-yl}methanol

700

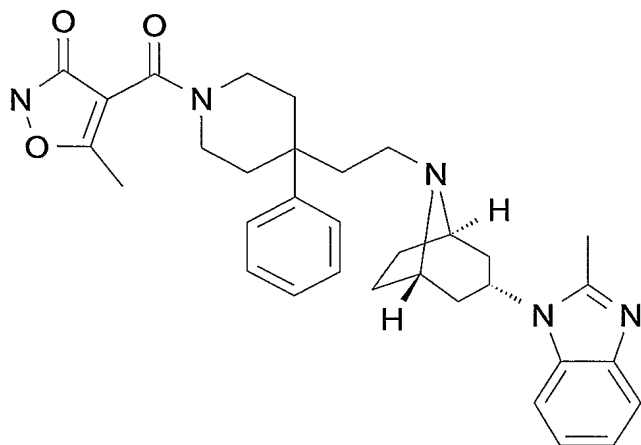
Example 961

3-methyl-1-[1-methyl-2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethyl]pyrrolidine-2,5-dione

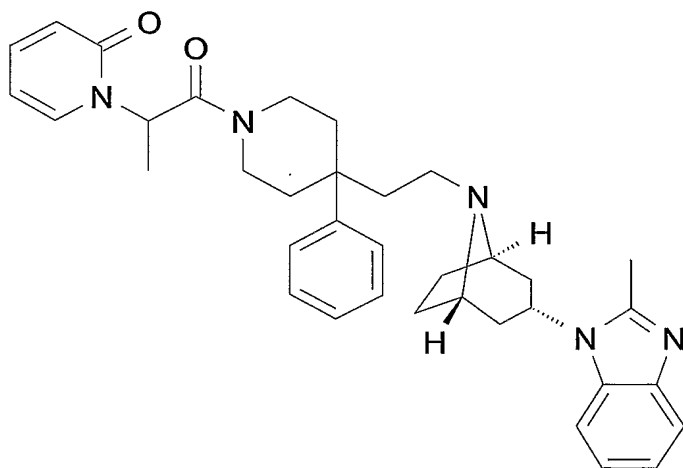
Example 962

5-methyl-4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]isoxazol-3(2H)-one

701

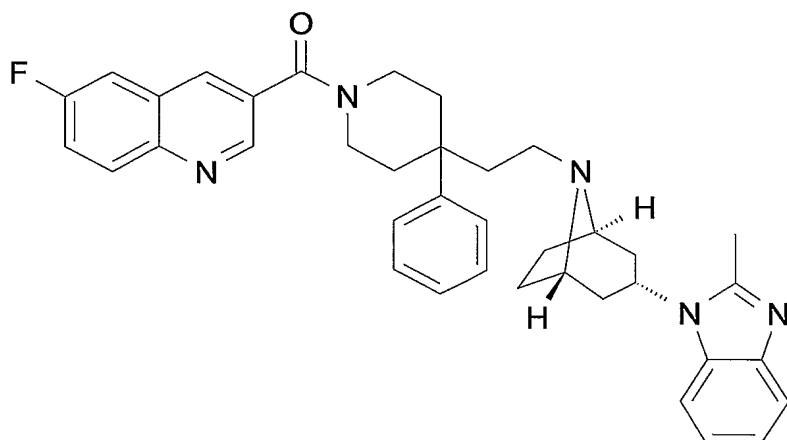
**Example 963**

1-[1-methyl-2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethyl]pyridin-2(1H)-one

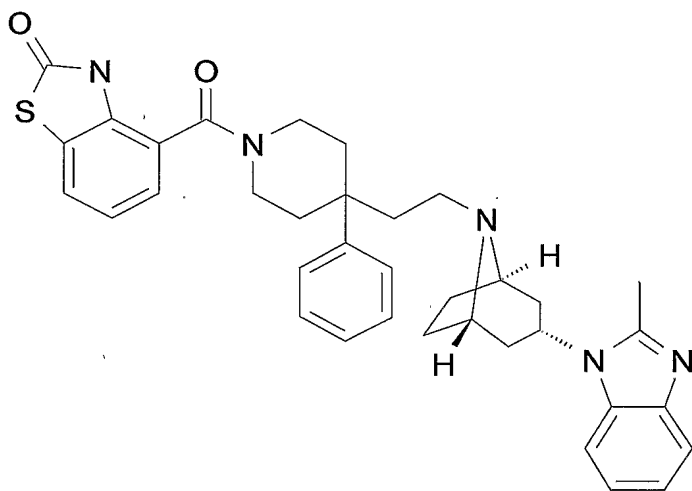
**Example 964**

6-fluoro-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]quinoline

702

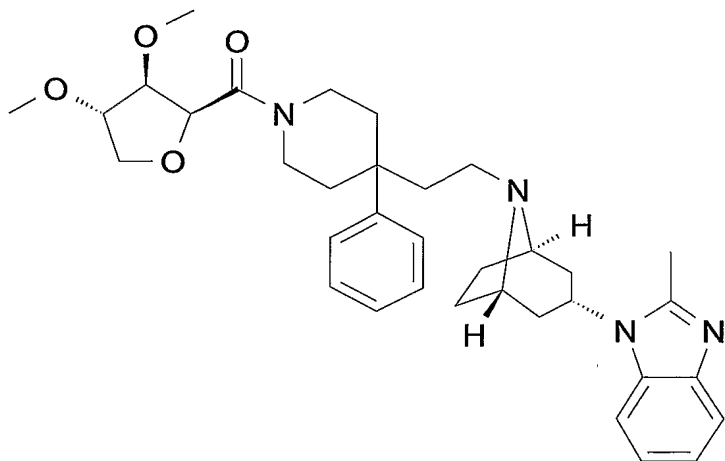
Example 965

4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,3-benzothiazol-2(3H)-one

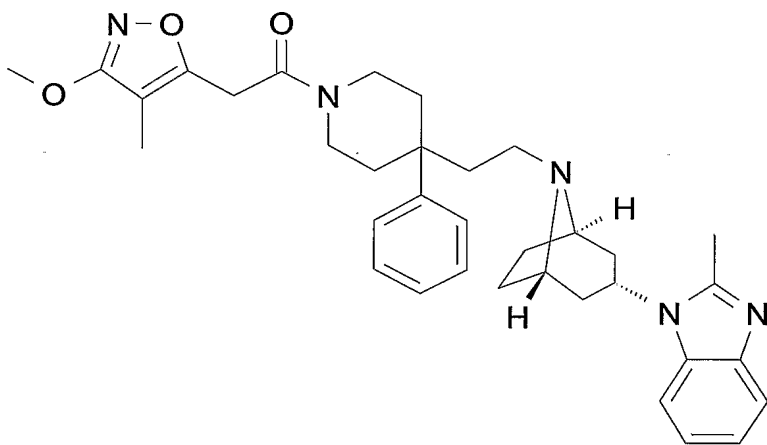
Example 966

1-((1R,5S)-8-{2-[1-((3S,4S)-3,4-dimethoxy-(2S)-tetrahydrofuran-2-carbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

703

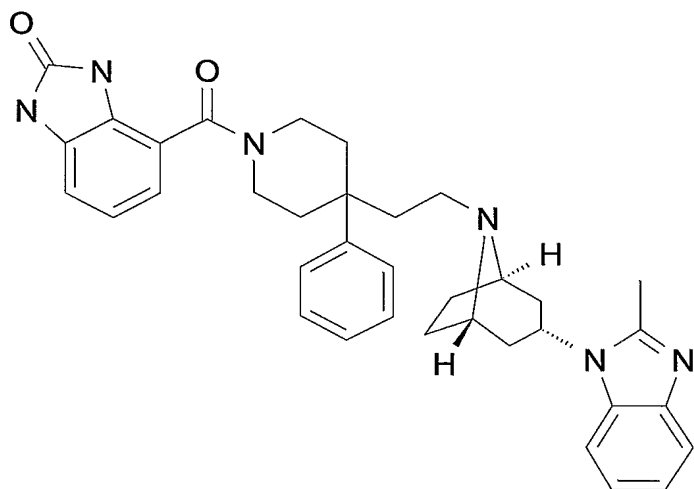
Example 967

1-[(1R,5S)-8-(2-{1-[(3-methoxy-4-methylisoxazol-5-yl)acetyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

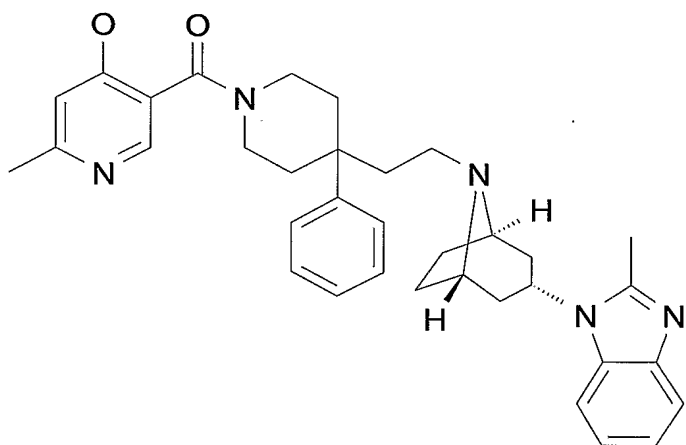
Example 968

4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,3-dihydro-2H-benzimidazol-2-one

704

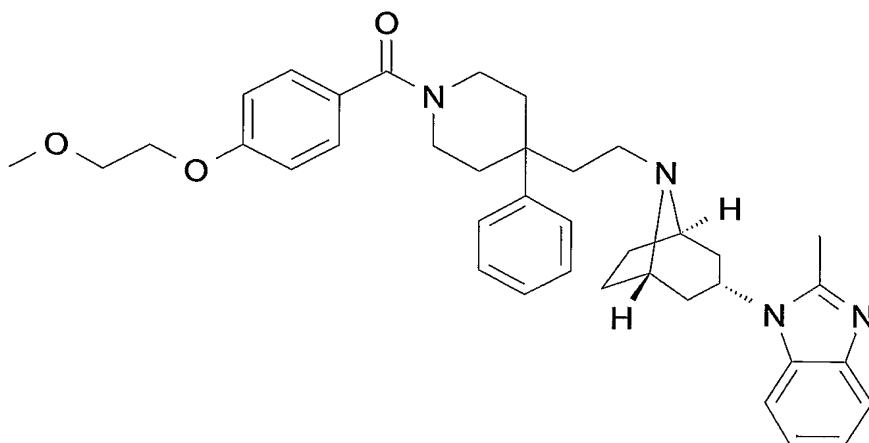
**Example 969**

2-methyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyridin-4-ol

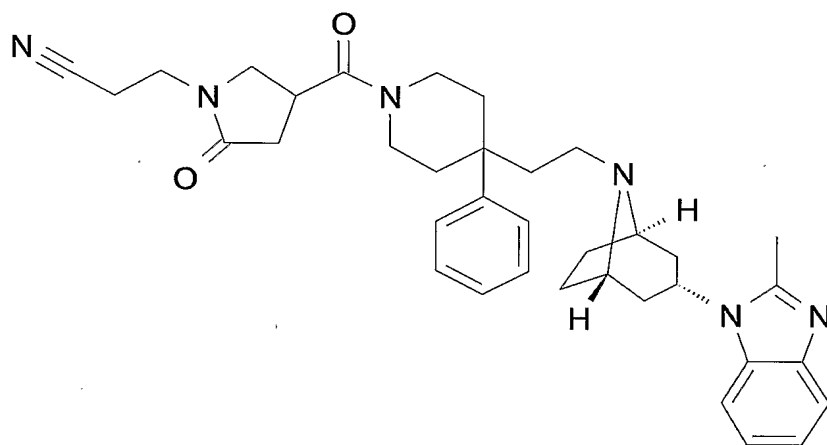
**Example 970**

1-[(1R,5S)-8-(2-{1-[4-(2-methoxyethoxy)benzoyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

705

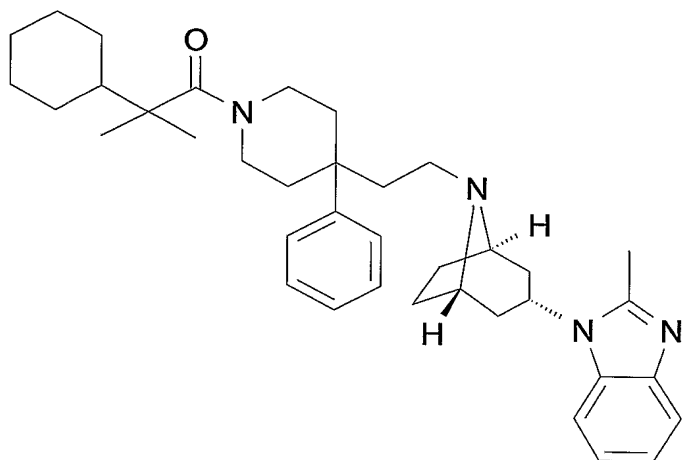
**Example 971**

3-{4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-2-oxopyrrolidin-1-yl}propanenitrile

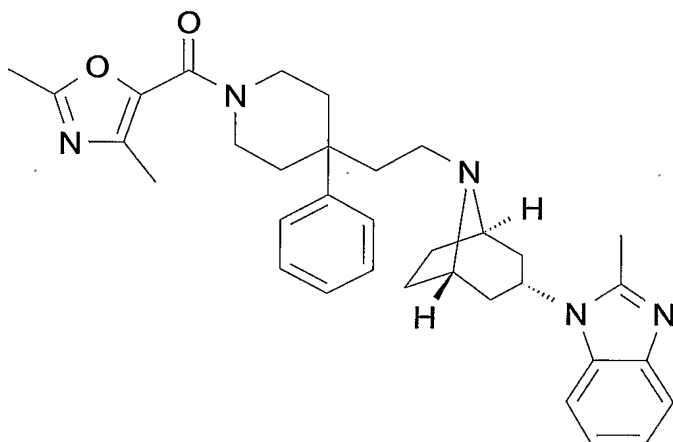
**Example 972**

1-((1R,5S)-8-{2-[1-(2-cyclohexyl-2-methylpropanoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

706

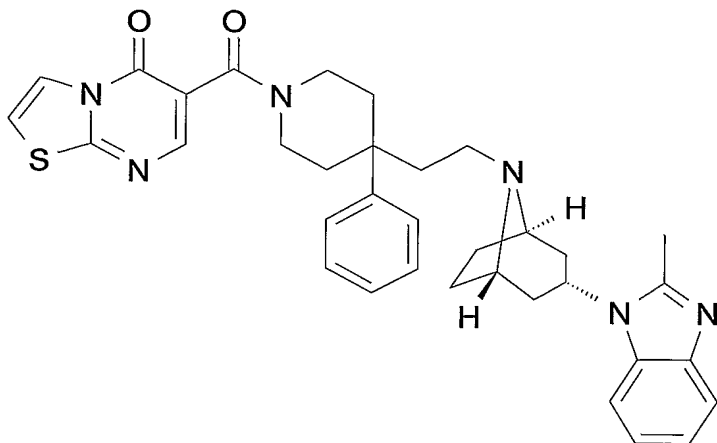
Example 973

1-[(1R,5S)-8-(2-{1-[(2,4-dimethyl-1,3-oxazol-5-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

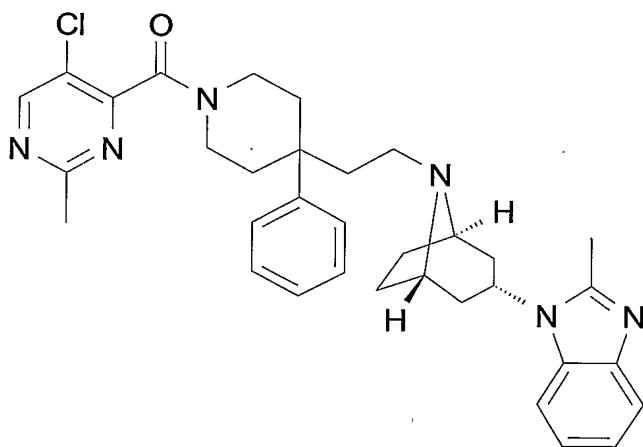
Example 974

6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-5H-[1,3]thiazolo[3,2-a]pyrimidin-5-one

707

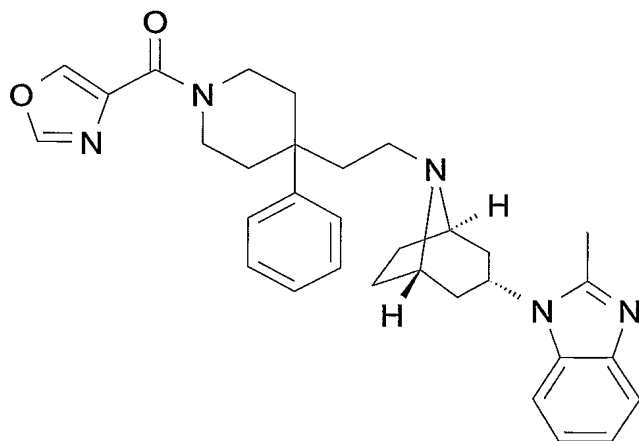
**Example 975**

1-[(1R,5S)-8-(2-{1-[(5-chloro-2-methylpyrimidin-4-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

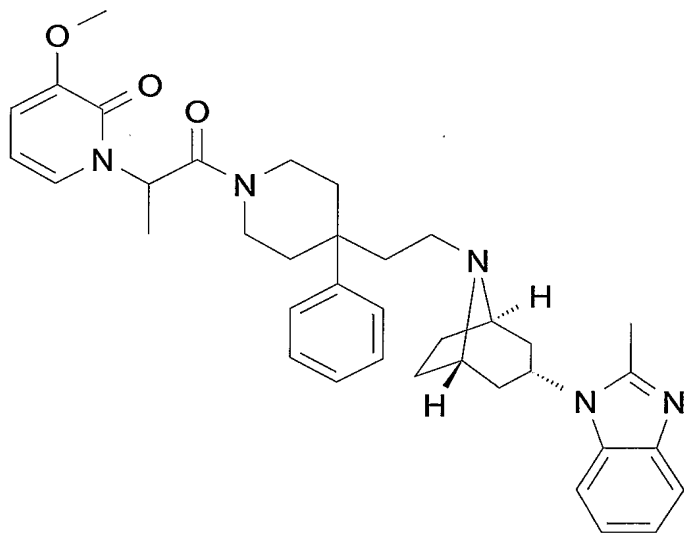
**Example 976**

2-methyl-1-((1R,5S)-8-{2-[1-(1,3-oxazol-4-ylcarbonyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole

708

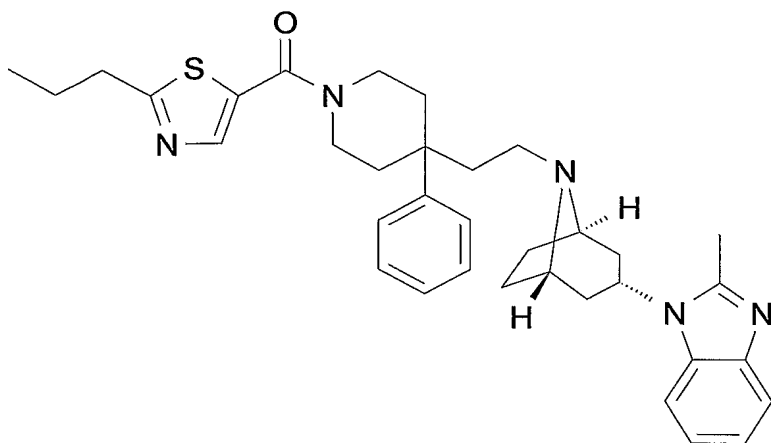
**Example 977**

3-methoxy-1-[1-methyl-2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethyl]pyridin-2(1H)-one

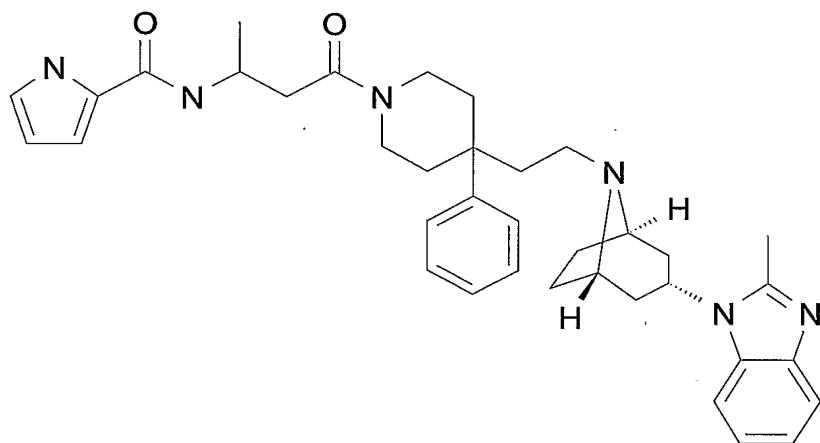
**Example 978**

2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[(2-propyl-1,3-thiazol-5-yl)carbonyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole

709

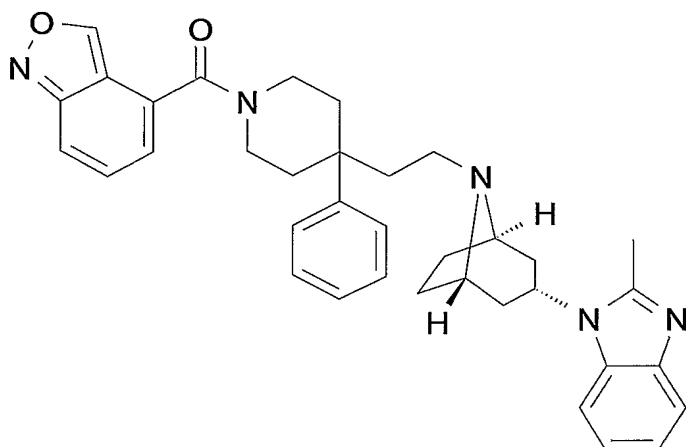
**Example 979**

N-[1-methyl-3-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-3-oxopropyl]-1H-pyrrole-2-carboxamide

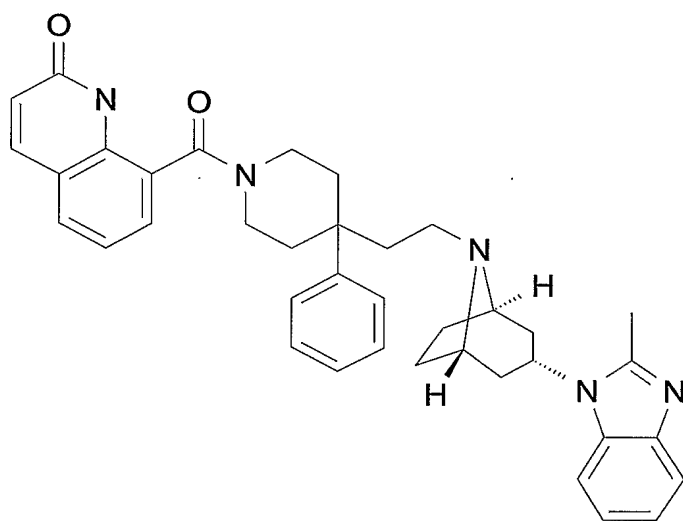
**Example 980**

4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-2,1-benzisoxazole

710

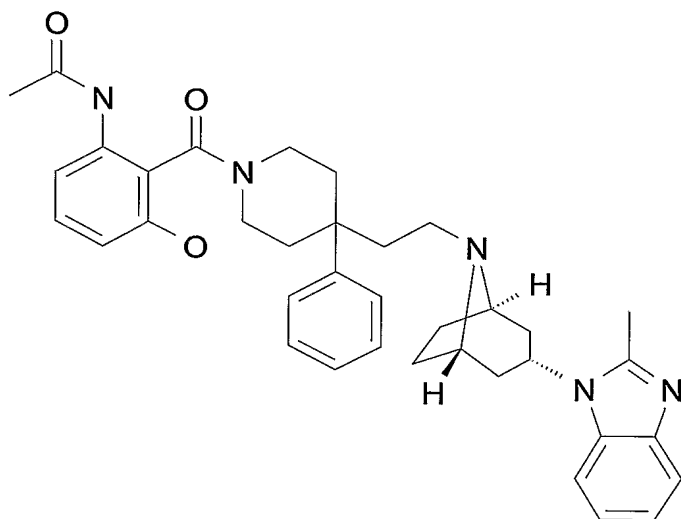
**Example 981**

8-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]quinolin-2(1H)-one

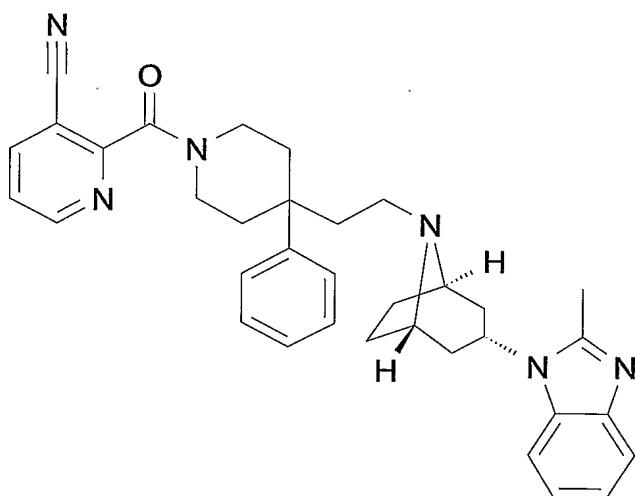
**Example 982**

N-{3-hydroxy-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}acetamide

711

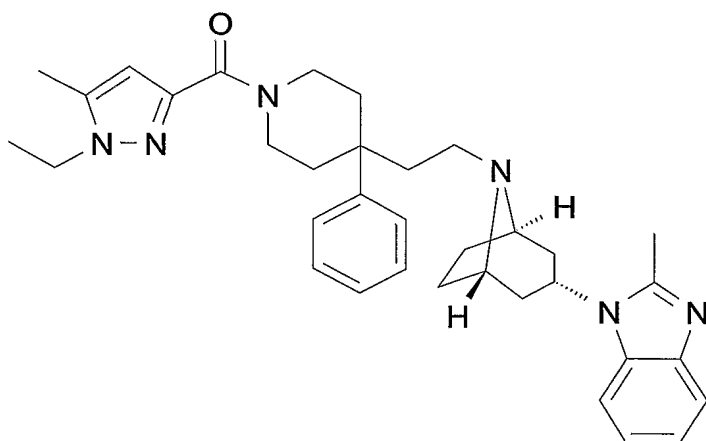
**Example 983**

2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]nicotinonitrile

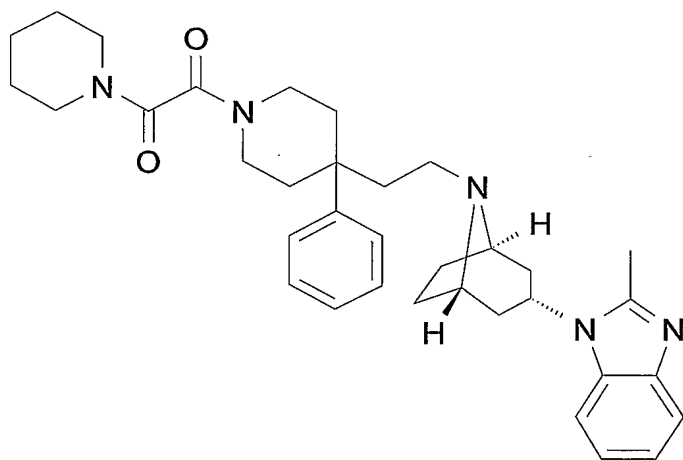
**Example 984**

1-[(1R,5S)-8-(2-{1-[(1-ethyl-5-methyl-1H-pyrazol-3-yl)carbonyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

712

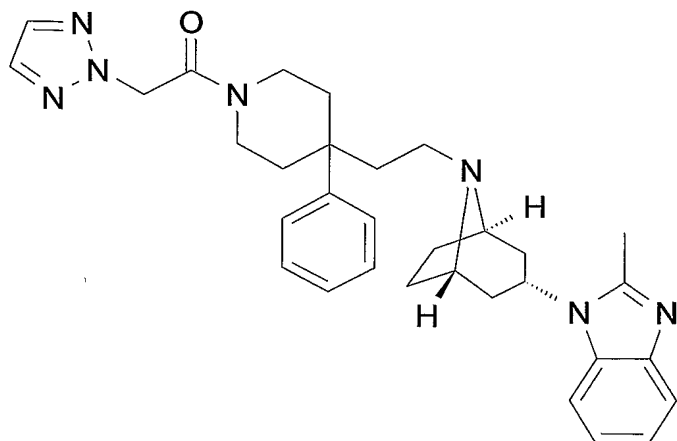
**Example 985**

2-methyl-1-[(1R,5S)-8-(2-{1-[oxo(piperidin-1-yl)acetyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole

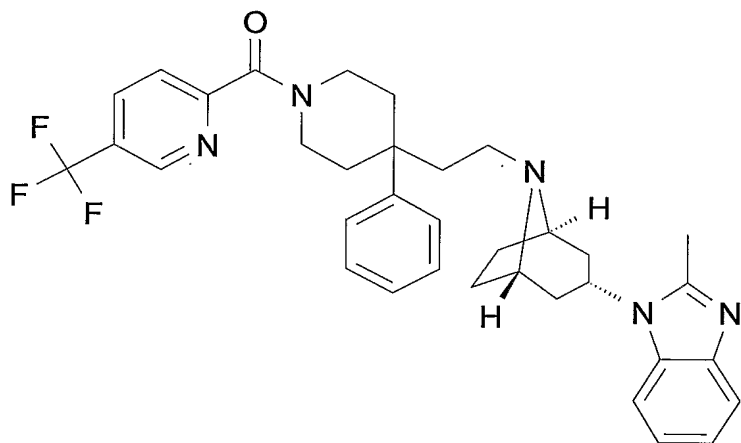
**Example 986**

2-methyl-1-((1R,5S)-8-{2-[4-phenyl-1-(2H-1,2,3-triazol-2-yl)acetyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl)-1H-benzimidazole

713

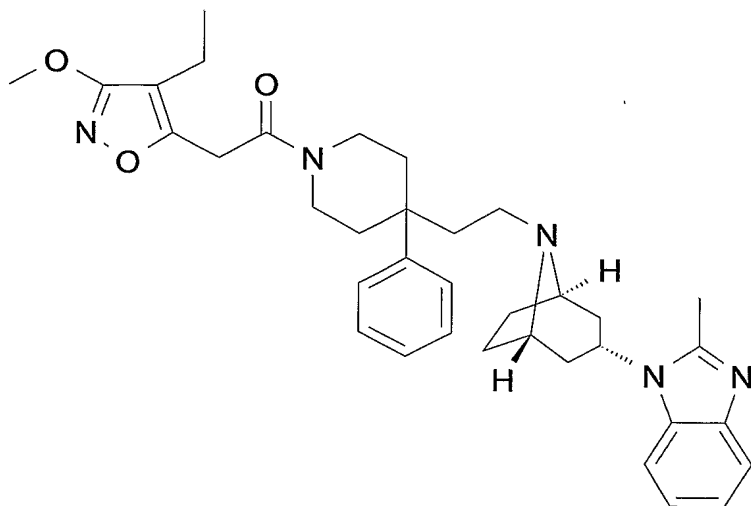
**Example 987**

2-methyl-1-[(1R,5S)-8-[2-(4-phenyl-1-[[5-(trifluoromethyl)pyridin-2-yl]carbonyl]piperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole

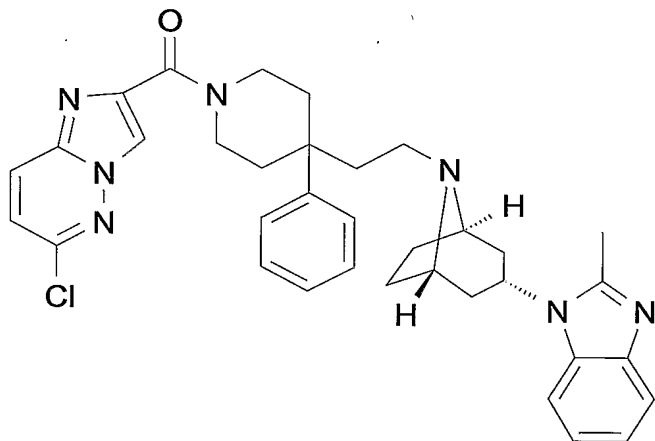
**Example 988**

1-[(1R,5S)-8-(2-{1-[(4-ethyl-3-methoxyisoxazol-5-yl)acetyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

714

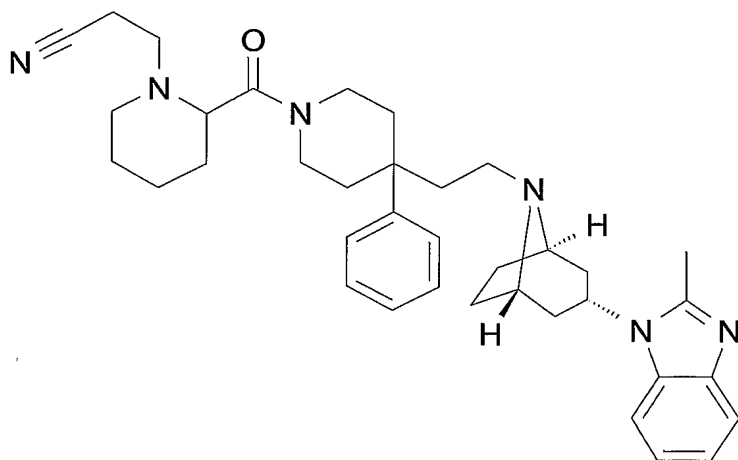
Example 989

6-chloro-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]imidazo[1,2-b]pyridazine

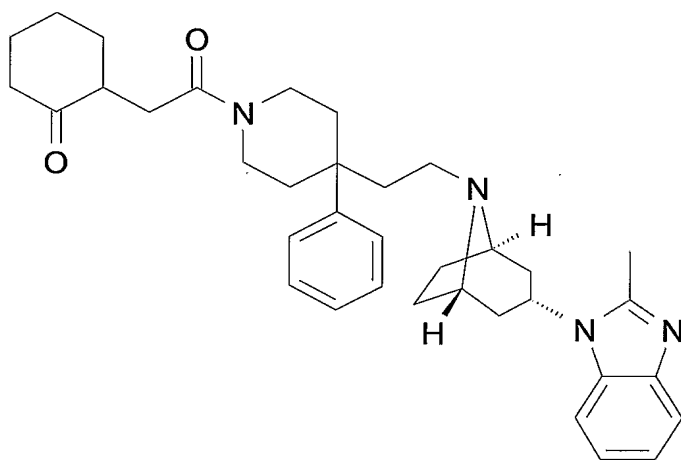
Example 990

3-{2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]piperidin-1-yl}propanenitrile

715

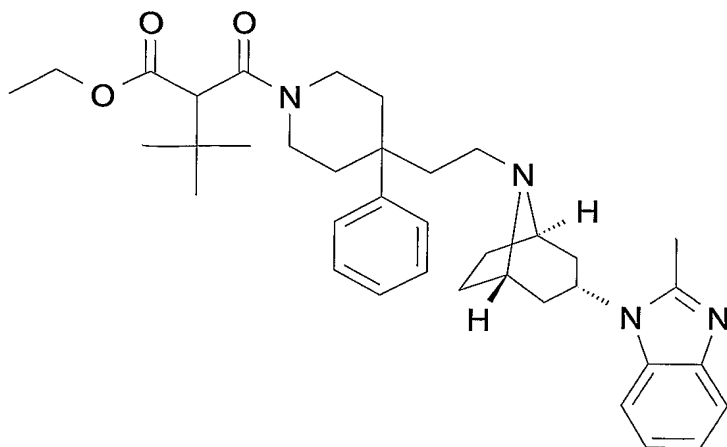
**Example 991**

2-[2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethyl]cyclohexanone

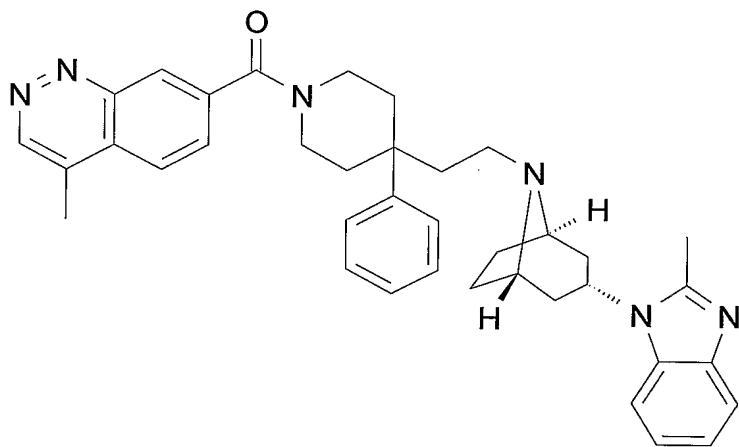
**Example 992**

ethyl 3,3-dimethyl-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]butanoate

716

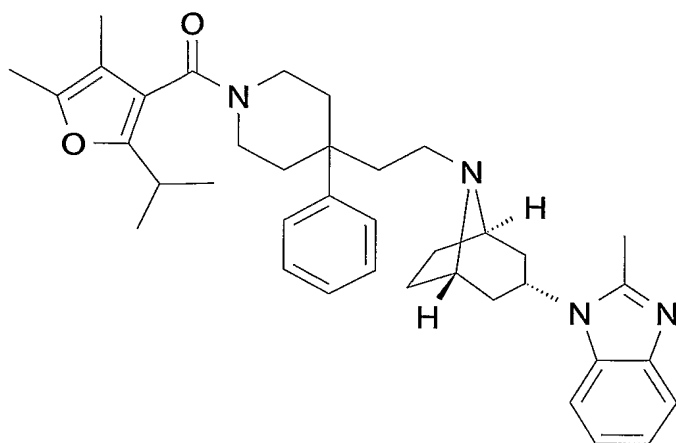
**Example 993**

4-methyl-7-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]cinnoline

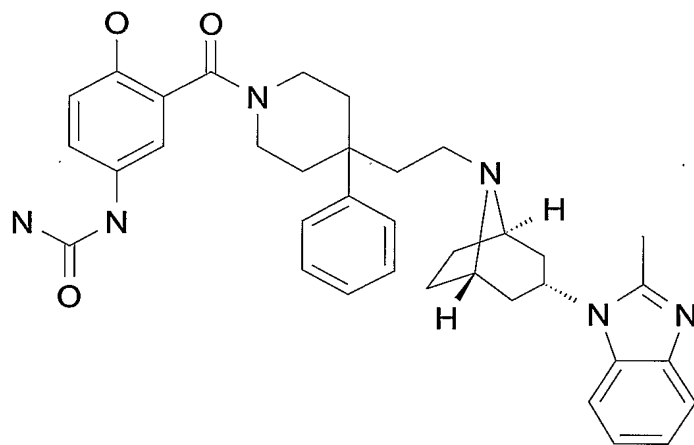
**Example 994**

1-((1R,5S)-8-{2-[1-(2-isopropyl-4,5-dimethyl-3-furoyl)-4-phenylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

717

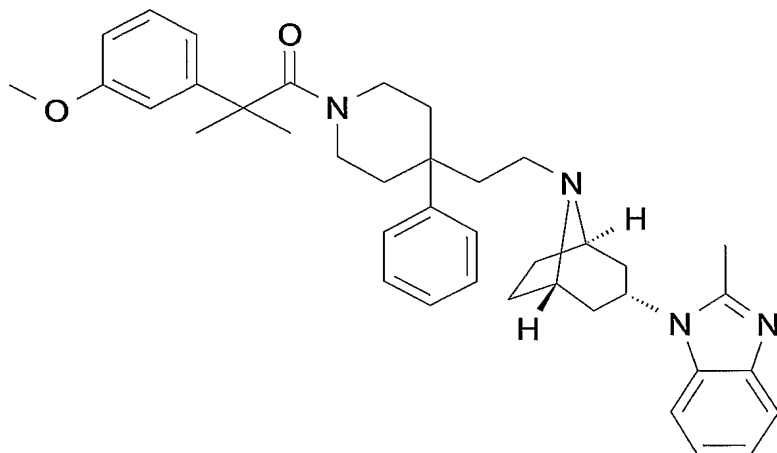
**Example 995**

N-{4-hydroxy-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]phenyl}urea

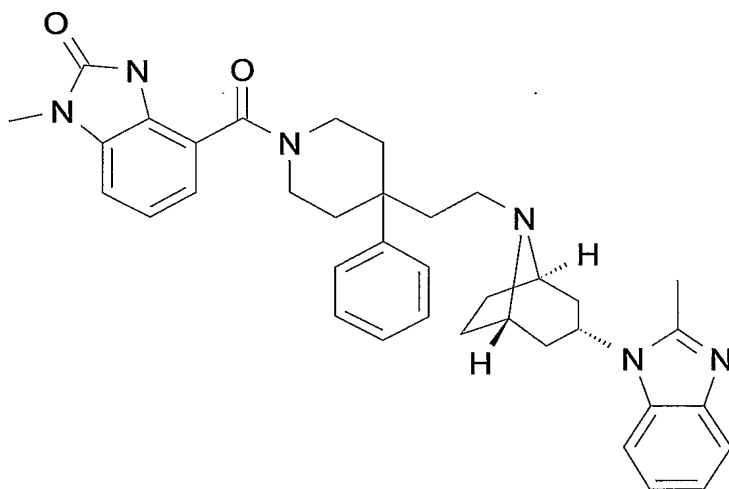
**Example 996**

1-[(1R,5S)-8-(2-{1-[2-(3-methoxyphenyl)-2-methylpropanoyl]-4-phenylpiperidin-4-yl]ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

718

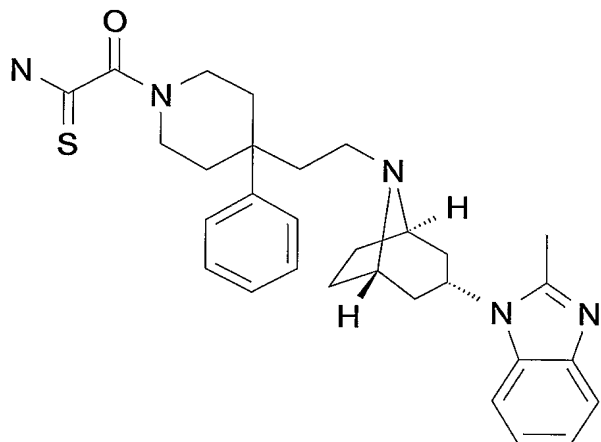
**Example 997**

1-methyl-4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,3-dihydro-2H-benzimidazol-2-one

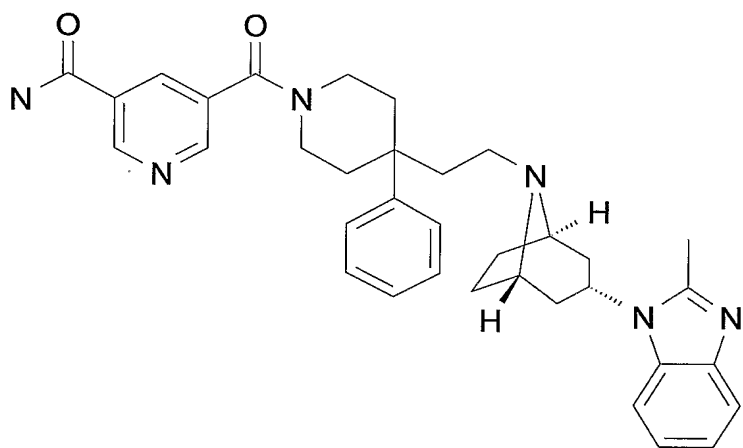
**Example 998**

2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethanethioamide

719

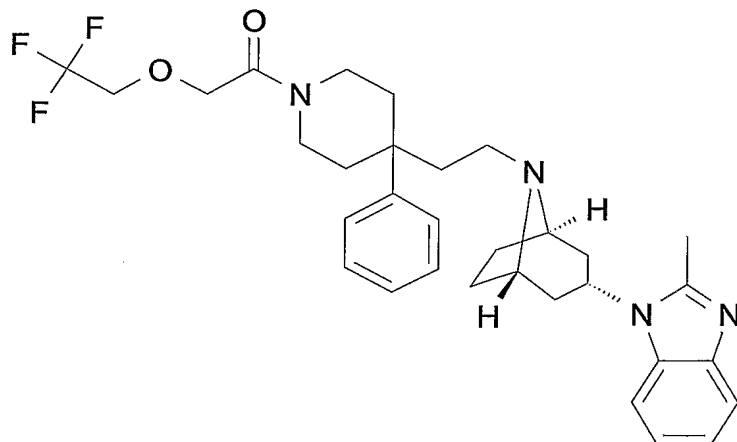
**Example 999**

5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]nicotinamide

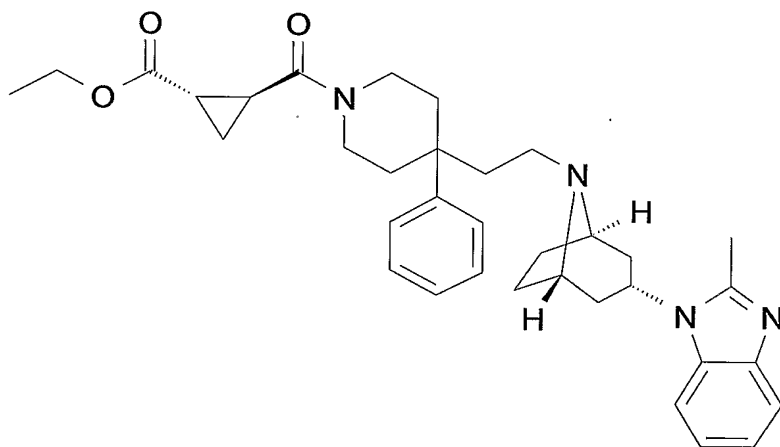
**Example 1000**

2-methyl-1-[(1R,5S)-8-(2-{4-phenyl-1-[(2,2,2-trifluoroethoxy)acetyl]piperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-1H-benzimidazole

720

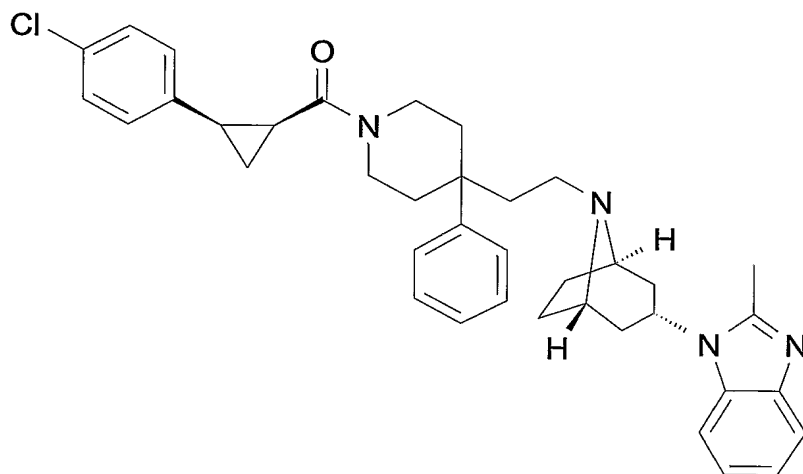
**Example 1001**

ethyl (1S,2S)-2-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]cyclopropanecarboxylate

**Example 1002**

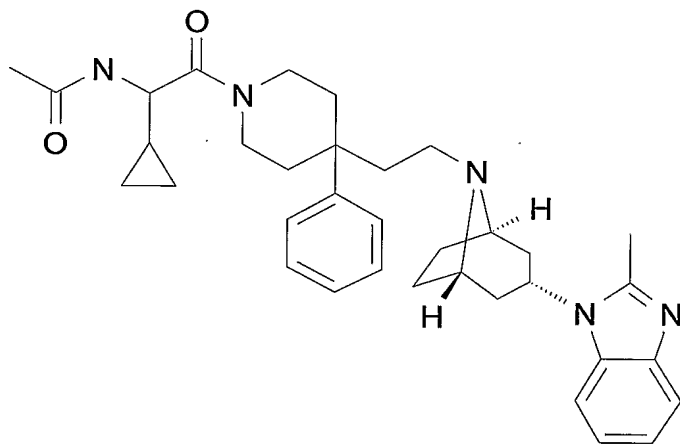
1-[(1R,5S)-8-[2-(1-[[[(1S,2R)-2-(4-chlorophenyl)cyclopropyl]carbonyl]-4-phenylpiperidin-4-yl]ethyl]-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole

721



Example 1003

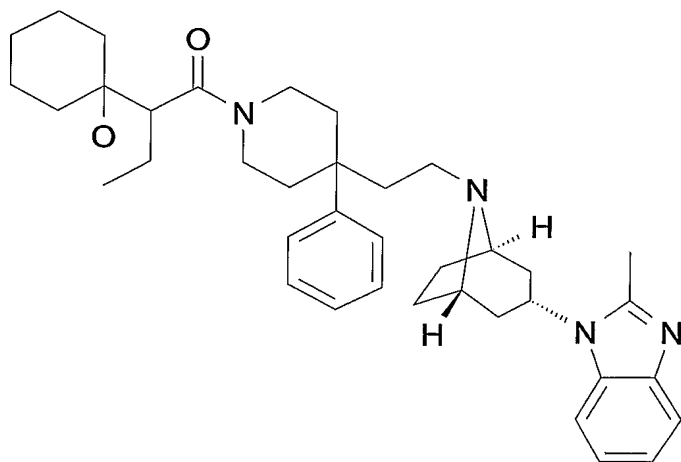
N-[1-cyclopropyl-2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethyl]acetamide



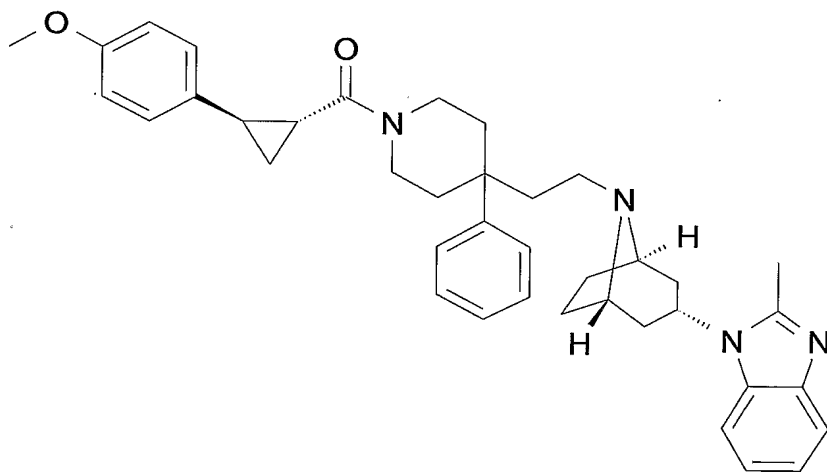
Example 1004

1-{1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]propyl}cyclohexanol

722

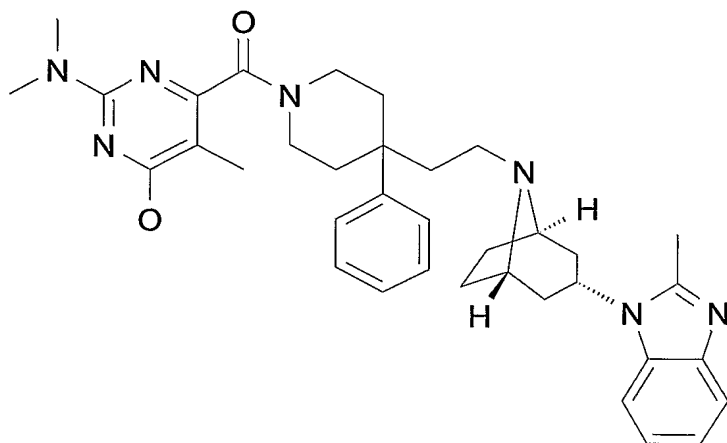
**Example 1005**

1-((1R,5S)-8-[2-(1-((1R,2R)-2-(4-methoxyphenyl)cyclopropyl)carbonyl)-4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole

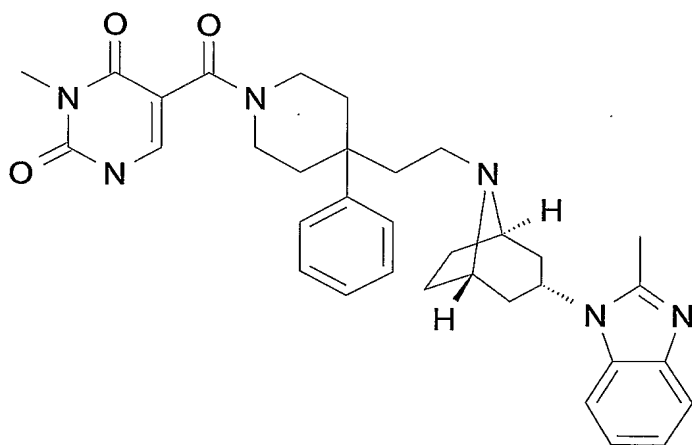
**Example 1006**

2-(dimethylamino)-5-methyl-6-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyrimidin-4-ol

723

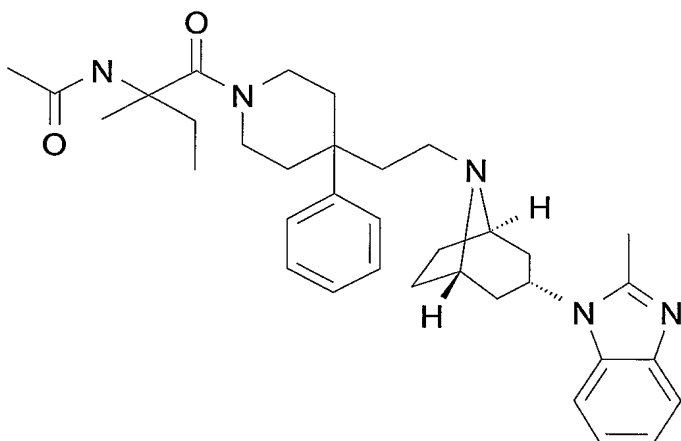
**Example 1007**

3-methyl-5-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyrimidine-2,4(1H,3H)-dione

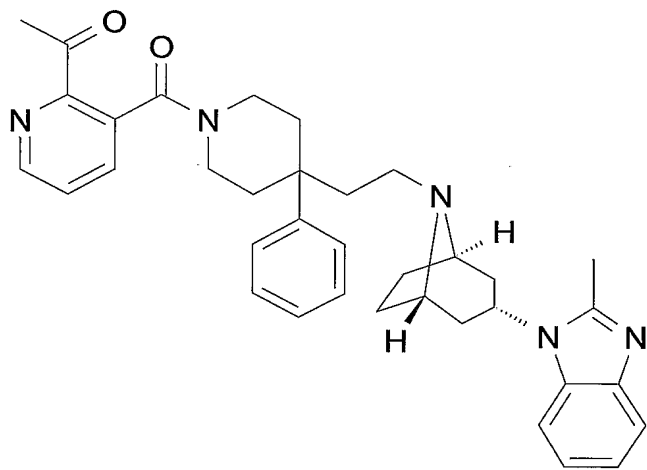
**Example 1008**

N-{1-methyl-1-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]propyl}acetamide

724

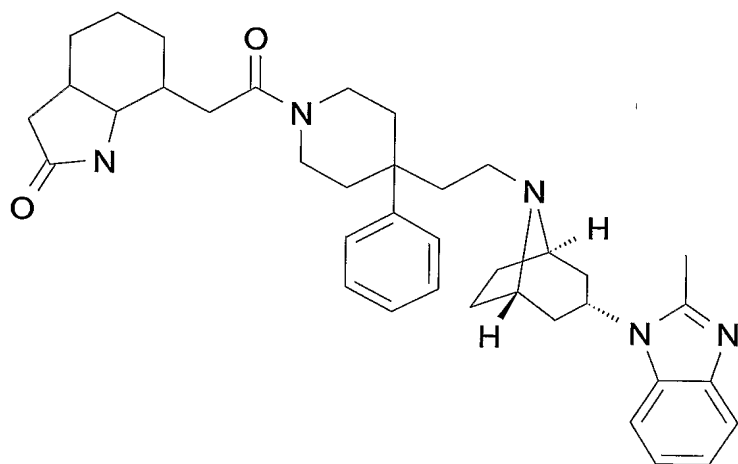
**Example 1009**

1-{3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]pyridin-2-yl}ethanone

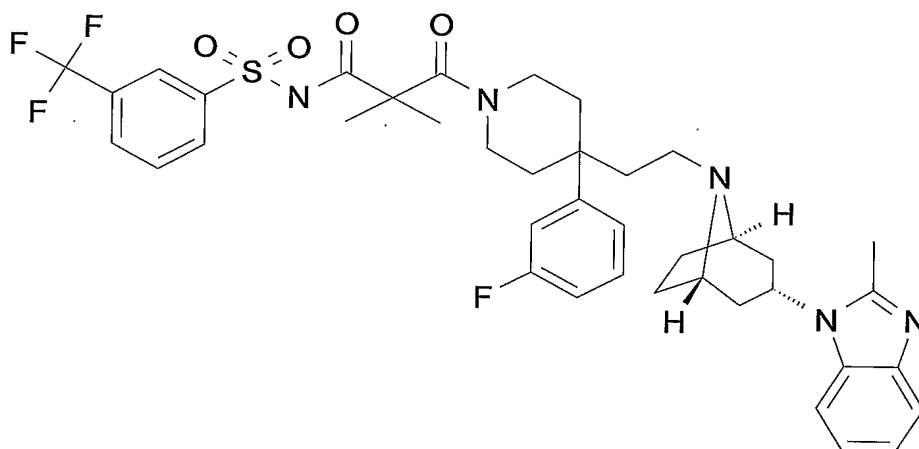
**Example 1010**

7-[2-(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)-2-oxoethyl]octahydro-2H-indol-2-one

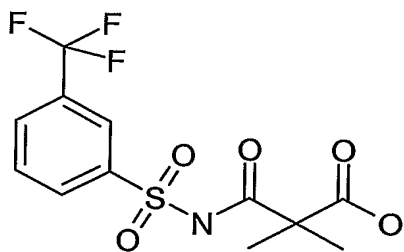
725

Example 1011

3-(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxo-N-[[3-(trifluoromethyl)phenyl]sulfonyl]propanamide



Synthesis of 2,2-dimethyl-3-oxo-3-({[3-(trifluoromethyl)phenyl]sulfonyl}amino)propanoic acid

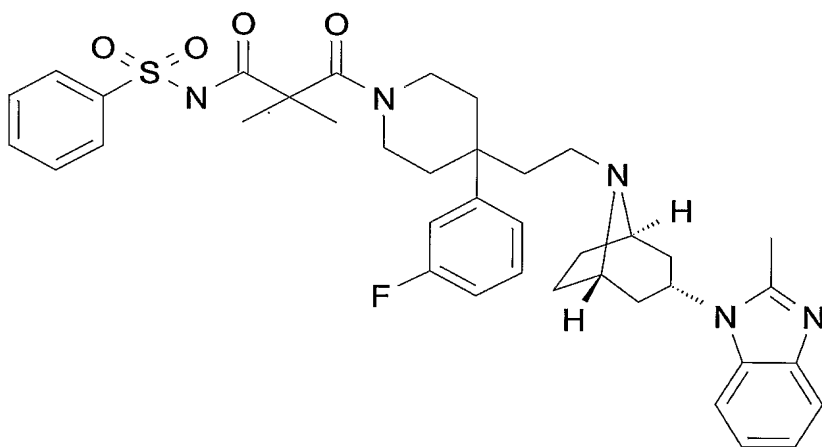


2,2-dimethyl-3-oxo-3-([3-(trifluoromethyl)phenyl]sulfonyl)amino)propanoic acid was prepared in the same manner as 2,2-dimethyl-3-oxo-3-[(phenylsulfonyl)amino]propanoic acid starting from 3-(trifluoromethyl)benzenesulfonyl chloride.

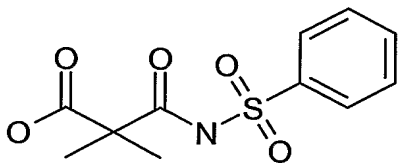
^1H NMR (300MHz, Chloroform- D_1) δ ppm 1.4 (m,6H) 5.1 (m,1H) 7.9 (M, 1H) 8.1 (m, 1H) 8.2 (m, 1H) 8.3 (m, 1H) 10.0 (s, 1H), Electrospray LC-MS 362 (M+23)

Example 1012

3-(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxo-N-(phenylsulfonyl)propanamide



The synthesis of 2,2-dimethyl-3-oxo-3-[(phenylsulfonyl)amino]propanoic acid



Benzenesulfonamide was made by adding benzenesulfonyl chloride to a solution of ammonia in tetrahydrofuran and evaporating to a solid.

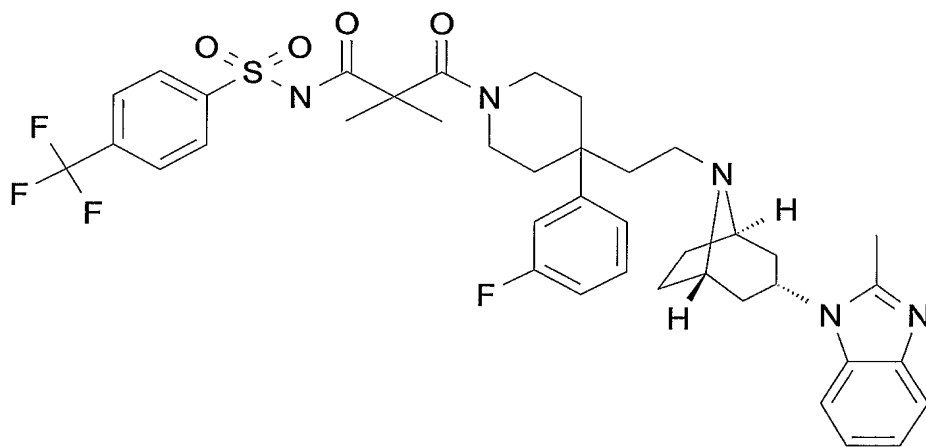
Benzenesulfonamide (87 mg, .50 mmole) was added to a shaken suspension

of 3-ethoxy-2,2-dimethyl-3-oxopropanoic acid (100 mg, .62 mmole) reactivated on PS-DCC resin (1.62 g, 1.25 mmole) and 1.50 mmole of *N,N*-dimethylpyridin-4-amine in DCE. When reaction is complete the resin is filtered off and the organic layer washed with 1N HCl dried and evaporated. The resulting residue was dissolved in 6 ml of ethanol and 6 ml of 1N LiOH was added and heated to 40 C°. The reaction was neutralized with 1N HCl and evaporated to afford 2,2-dimethyl-3-oxo-3-[(phenylsulfonyl)amino]propanoic acid as a crude product which was used with no further purification.

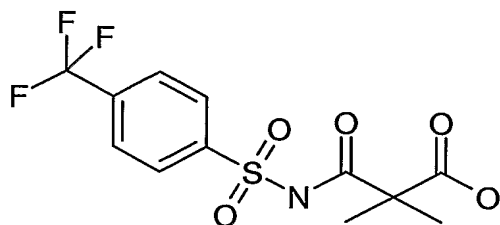
¹HNMR (300MHz, Chloroform-D1) δ ppm 1.4 (m, 6H) 4.9 (s, 1H) 7.6 (m, 3H) 7.9 (m, 1H) 8.1 (m, 1H) 9.8 (s, 1H), Electrospray LC-MS 180 (M+23).

Example 1013

3-(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxo-N-{[4-(trifluoromethyl)phenyl]sulfonyl}propanamide



The synthesis of 2,2-dimethyl-3-oxo-3-({[4-(trifluoromethyl)phenyl]sulfonyl}amino)propanoic acid

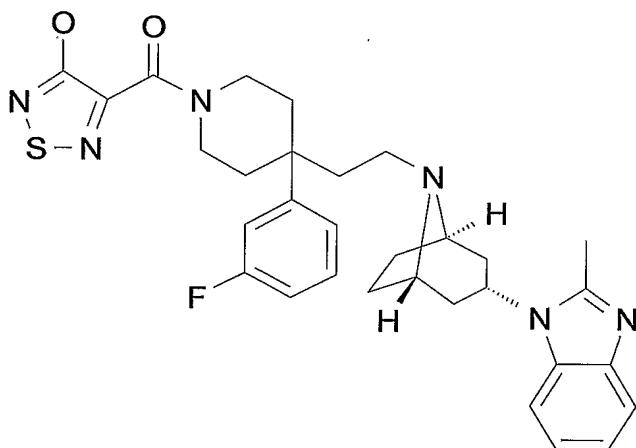


2,2-dimethyl-3-oxo-3-([4-(trifluoromethyl)phenyl]sulfonylamino)propanoic acid was prepared in the same manner as 2,2-dimethyl-3-oxo-3-[(phenylsulfonyl)amino]propanoic acid starting from 4-(trifluoromethyl)benzenesulfonyl chloride.

¹HNMR (300MHz, Chloroform-D1) δ ppm 1.4 (m, 6H) 5.1 (s, 1H) 7.8 (M, 2H) 8.1 (d, $J=8.78$ Hz, 1H) 8.2 (d, $J=9.0$ Hz, 1H) 9.9 (s, 1H)

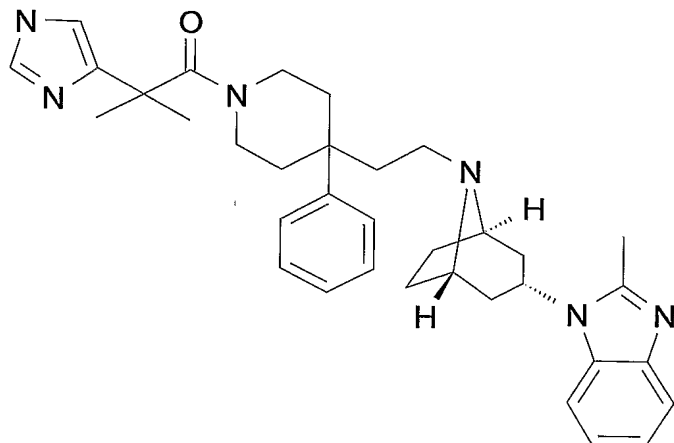
Example 1014

4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-1,2,5-thiadiazol-3-ol



Example 1015

1-[(1R,5S)-8-(2-{1-[2-(1H-imidazol-4-yl)-2-methylpropanoyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole



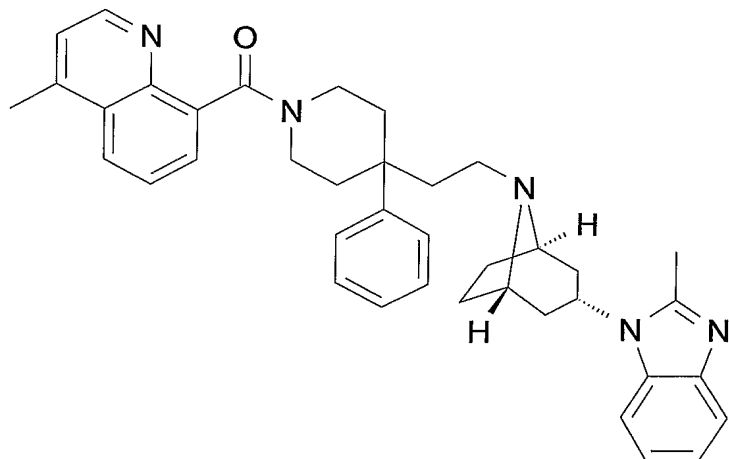
Using Method A (HATU) 2-(1*H*-imidazol-4-yl)-2-methylpropanoic acid and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1*H*-benzimidazole dihydrochloride were coupled to afford 1-[(1*R*,5*S*)-8-(2-{1-[2-(1*H*-imidazol-4-yl)-2-methylpropanoyl]-4-phenylpiperidin-4-yl}ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1*H*-benzimidazole 11.8 mg 42% yeild.

¹H NMR (400 MHz, DMSO-*D*₆) δ ppm 1.2 (m, 1 H) 1.5 (m, 8 H) 1.7 (m, 8 H) 2.3 (m, 2 H) 2.5 (m, 3 H) 2.5 (m, 8 H) 3.2 (m, 2 H) 4.5 (m, 1 H) 7.1 (m, 10 H) 11.9 (m, 1 H)

Electrospray LC-MS 565 (M+H)

Example 1016

4-methyl-8-[(4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]quinoline



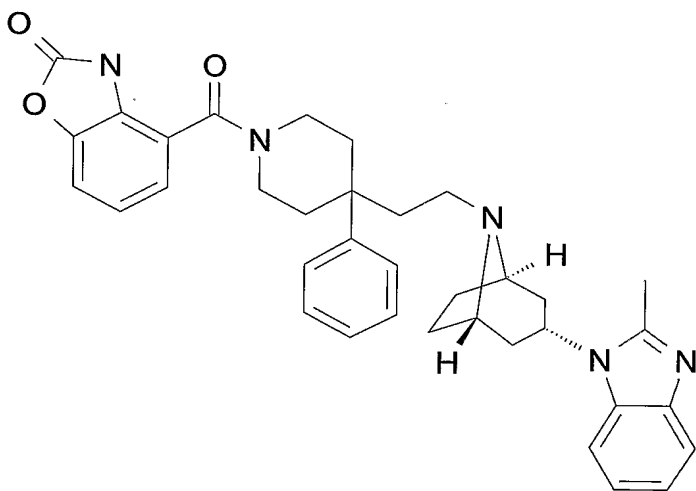
Using Method A (HATU) 4-methylquinoline-8-carboxylic acid and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride were coupled to afford 4-methyl-8-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]quinoline 14.8 mg 49% yeild.

¹H NMR (400 MHz, DMSO-D₆) d ppm 1.7 (m, 10 H) 2.1 (m, 2 H) 2.3 (m, 6 H) 2.7 (m, 3 H) 2.9 (m, 1 H) 3.2 (m, 4 H) 3.6 (m, 1 H) 4.0 (m, 1 H) 4.5 (m, 1 H) 7.1 (m, 2 H) 7.2 (m, J=2.9 Hz, 1 H) 7.4 (m, 6 H) 7.5 (m, J=5.4 Hz, 1 H) 7.6 (m, 2 H) 8.2 (m, J=5.7, 2.1 Hz, 1 H) 8.7 (m, 1 H)

Electrospray LC-MS 598 (M+H)

Example 1017

4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,3-benzoxazol-2(3H)-one



Using Method A (HATU) 2-oxo-2,3-dihydro-1,3-benzoxazole-4-carboxylic acid and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride were coupled to afford 4-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1,3-benzoxazol-2(3H)-one 8.7 mg 30% yeild.

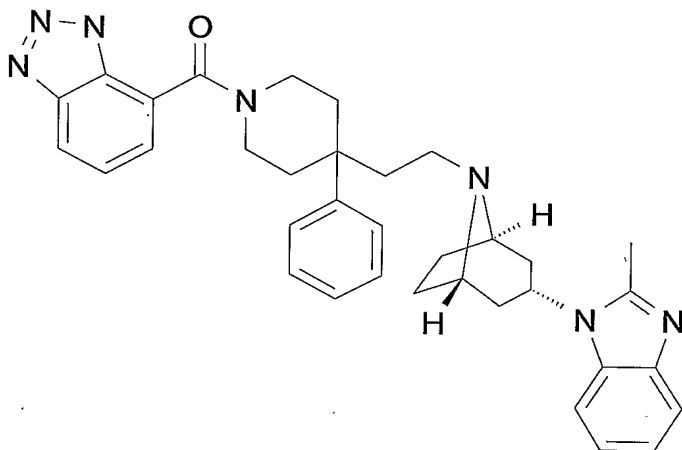
731

¹H NMR (400 MHz, DMSO-D₆) δ ppm 1.6 (m, 2 H) 1.8 (m, 9 H) 2.4 (m, 2 H) 2.4 (m, 3 H) 2.5 (m, 7 H) 3.2 (m, 3 H) 4.5 (m, 1 H) 7.2 (m, 5 H) 7.4 (m, 6 H) 7.5 (m, 1 H)

Electrospray LC-MS 590 (M+H)

Example 1018

7-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1H-1,2,3-benzotriazole



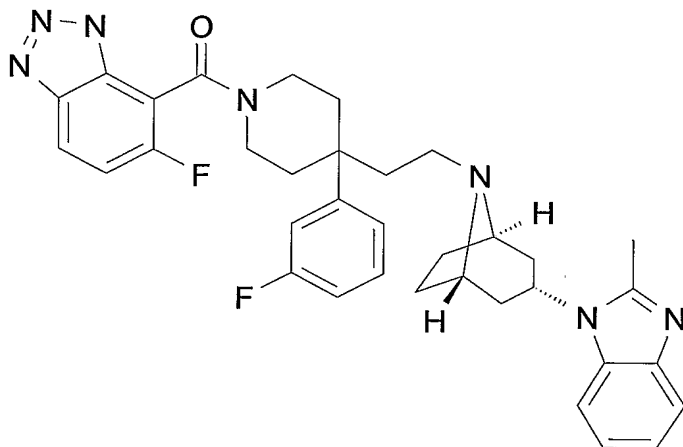
Using Method A (HATU) 1H-1,2,3-benzotriazole-7-carboxylic acid and endo 2-methyl-1-{8-[2-(4-phenylpiperidin-4-yl)ethyl]-8-azabicyclo[3.2.1]oct-3-yl}-1H-benzimidazole dihydrochloride were coupled to afford 7-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]-1H-1,2,3-benzotriazole 9.9 mg 34% yield.

¹H NMR (400 MHz, DMSO-D₆) δ ppm 1.6 (m, 1 H) 1.8 (m, 8 H) 2.4 (m, 4 H) 2.5 (m, 8 H) 3.2 (m, 3 H) 4.0 (m, 1 H) 4.5 (m, 1 H) 7.1 (m, 2 H) 7.2 (m, 1 H) 7.4 (m, 8 H) 8.0 (m, 1 H)

Electrospray LC-MS 574 (M+H)

Example 1019

6-fluoro-7-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-1H-1,2,3-benzotriazole

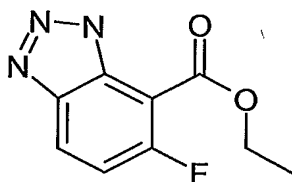


Using Method A (HATU) 6-fluoro-1H-1,2,3-benzotriazole-7-carboxylic acid and endo-1-(8-{2-[4-(3-fluorophenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride were coupled to afford 6-fluoro-7-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-1H-1,2,3-benzotriazole 83.9 mg 62% yield.

¹H NMR (400 MHz, METHANOL-D₄) δ ppm 1.7 (m, 1 H) 2.0 (m, 4 H) 2.4 (m, 4 H) 2.8 (m, 3 H) 3.4 (m, 13 H) 4.7 (m, 1 H) 7.2 (m, 10 H) 7.9 (m, 1 H)

Electrospray LC-MS 610 (M+H)

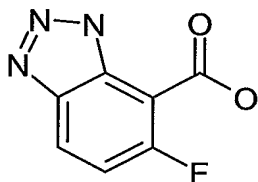
Preparation of the ethyl 6-fluoro-1H-1,2,3-benzotriazole-7-carboxylate



ethyl 2,3-diamino-6-fluorobenzoate (1.00 g, 5.04 mmole) in 50 ml of water and 10 ml acetic acid was cooled to $-10\text{ }^{\circ}\text{C}$. To this solution was added dropwise sodium nitrite (348 mg, 5.04 mmole) in 30 ml of water. After the addition the reaction was warmed to $0\text{ }^{\circ}\text{C}$ for 30 min, then to room temperature for 1 hr, and finally $50\text{ }^{\circ}\text{C}$ for 1 hr. The reaction was filtered after stirring over night and washed with water. The dark brownish purple solid was dissolved in ethylacetate dried over magnesium sulfate and evaporated to afford ethyl 6-fluoro-1*H*-1,2,3-benzotriazole-7-carboxylate (920 mg, 87% yield)

^1H NMR (400 MHz, METHANOL- D_4) δ ppm 1.3 (t, $J=7.1$ Hz, 3 H) 4.4 (q, $J=7.0$ Hz, 2 H) 7.2 (dd, $J=11.2, 9.0$ Hz, 1 H) 8.1 (dd, $J=9.1, 4.1$ Hz, 1 H)

Preparation of the 6-fluoro-1*H*-1,2,3-benzotriazole-7-carboxylic acid

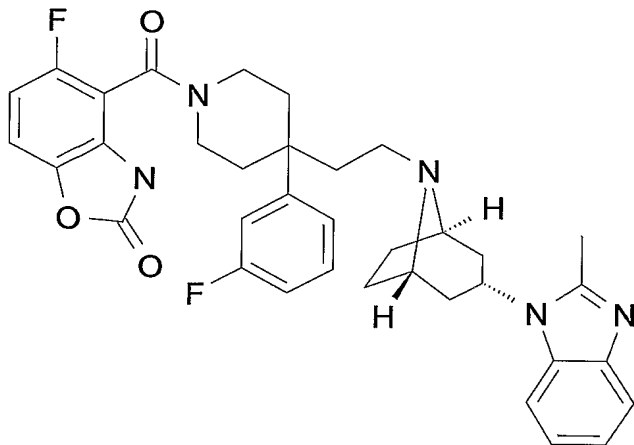


ethyl 6-fluoro-1*H*-1,2,3-benzotriazole-7-carboxylate (920 mg) was heated in 6*N* HCl until all of the starting material disappeared. Evaporation of the HCl afforded 718 mg of a brownish solid.

^1H NMR (300 MHz, DMSO- D_6) δ ppm 7.4 (dd, $J=11.2, 9.0$ Hz, 1 H) 8.3 (dd, $J=9.1, 4.1$ Hz, 1 H)

Example 1020

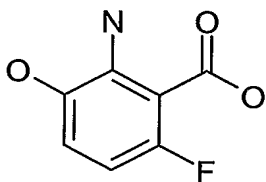
5-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-1,3-benzoxazol-2(3*H*)-one



Using Method A (HATU) 5-fluoro-2-oxo-2,3-dihydro-1,3-benzoxazole-4-carboxylic acid and endo-1-(8-{2-[4-(3-fluorophenyl) piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride were coupled to afford 5-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]-1,3-benzoxazol-2(3H)-one. ¹H NMR (300 MHz, METHANOL-D₄) δ ppm 1.4 (d, J=6.5 Hz, 1 H) 1.8 (m, 3 H) 2.0 (m, 8 H) 2.2 (m, 3 H) 2.5 (m, 3 H) 3.0 (m, 3 H) 3.5 (m, 4 H) 4.2 (m, 1 H) 7.0 (m, 2 H) 7.3 (m, 7 H) 7.6 (m, 1 H) 8.0 (m, 1 H) Electrospray LC-MS 626(M+H)

Preparation of

2-amino-6-fluoro-3-hydroxybenzoic acid

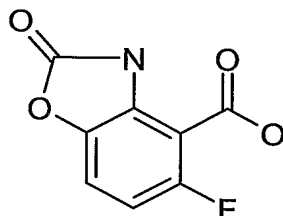


2-amino-6-fluorobenzoic acid (5.00 g, 32.2 mmole) was dissolved in 30 ml of 2N sodium hydroxide. To this was added dropwise a solution of sodium persulfate (7.67 g, 32.2 mmole) in 80 ml of water. After stirring over night the resulting black solution was extracted with 2 L of ether and 1 L of ethylacetate. Evaporation of the water gave a black solid that was used with no purification.

^1H NMR (400 MHz, DMSO- D_6) δ ppm 6.2 (dd, $J=11.5, 8.6$ Hz, 1 H) 6.7 (dd, $J=8.6, 4.9$ Hz, 1 H)

LC-MS

5-fluoro-2-oxo-2,3-dihydro-1,3-benzoxazole-4-carboxylic acid



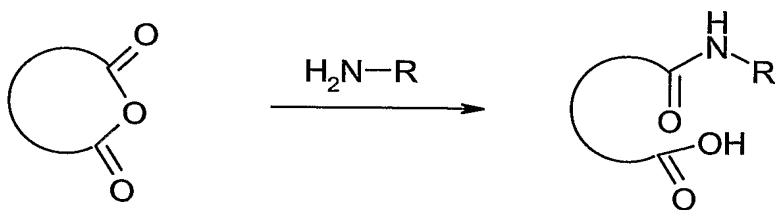
To a THF solution of 2-amino-6-fluoro-3-hydroxybenzoic acid (520 mg, 3.04 mmole) and *n,n*-diisopropylethylamine (942 mg, 7.29 mmole) was added bis(trichloromethyl) carbonate (1.08 g, 3.64 mmole) and stirred. Removal of solvent under vacuum afforded a residue, which was run on reversephase flash chromatography 10 to 90% acetonitrile water (0.01% TFA). The resulting fractions were evaporated.

APCI LC-MS 196 (M-H) 198 (M+H)

Examples below were synthesized as follows.

Method AA. Synthesis of functionalized carboxamide carboxylic acids via amination of cyclic anhydrides (Acids 69-79 and 97-153).

1mmol of anhydride was treated with 10mmol of either a 0.5M solution of NH_3 in Dioxane or a 2M solution of either methylamine, ethylamine, isopropylamine or cyclopropylamine in THF at 40°C in a sealed tube for 72h. The reaction mixtures were concentrated to remove solvent and excess amine to give the crude carboxamide carboxylic acid as the salt of the corresponding amine. Crude materials were used without further purification or characterization in the subsequent coupling reaction to generate final compounds.



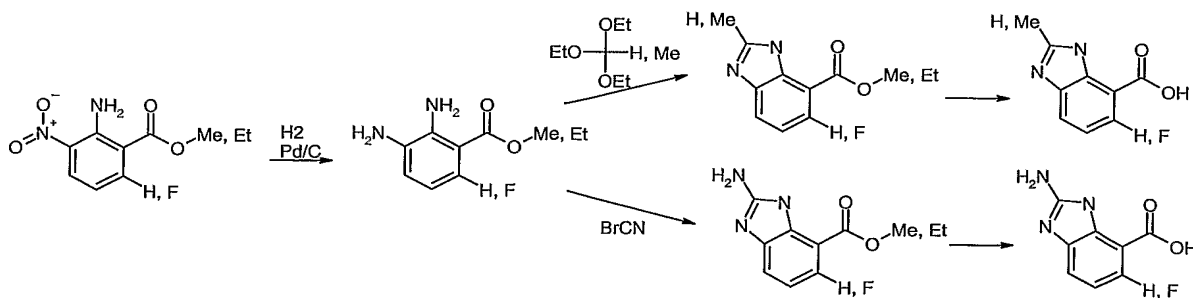
Method BB. Synthesis of benzimidazole carboxylic acids (Acids 65-68, 88, and 89)

Step 1: 50mmol of an appropriately substituted 2-amino-3-nitrobenzoic acid ester in 250mL of EtOH/EtOAc (1:1) was treated with 980mg of 10%Pd/C and $\text{H}_2(\text{g})$ (1atm) at ambient temperature for 16h. The catalyst was filtered off and the filtrate concentrated to give the corresponding dianiline as a crystalline solid in quantitative yield. The crude material was carried on to either step 2A or 2B without further purification.

Step 2A: 5.6mmol of the dianiline was treated with 15mL of either triethyl orthoacetate or triethyl orthoformate at 120°C for 16h. The reaction mixture was concentrated to dryness to give the corresponding benzimidazole as a crystalline solid that was carried on to step 3 without further purification.

Step2B: Alternatively, 6.0mmol of dianiline was treated with 6.3mmol BrCN in 15mL CH_3OH at reflux for 3h. The reaction mixture was cooled to ambient temperature and precipitate was filtered off to give the corresponding 2-aminobenzimidazole.

Step 3: Benzimidazoles obtained from steps 2A and 2B were treated with 6N HCl at 80°C for 8h. The reaction mixtures were concentrated to dryness to give the benzimidazole carboxylic acids which were used without purification in coupling reactions to yield final compounds.

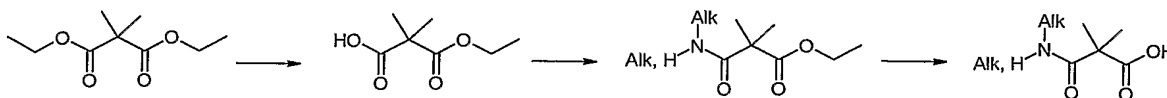


Method CC. Synthesis of carboxamide carboxylic acids by amination of dimethyl malonate (Acids 90-96).

Step 1: Diethyl dimethylpropanedioate (10g, 53mmol) in 170mL EtOH was treated with 3.00g (53mmol) KOH at ambient temperature for 4 days. The reaction mixture was concentrated to dryness and partitioned between EtOAc and water. The aqueous phase was isolated, combined with fresh EtOAc and the pH adj to 2 with 6N HCl. The organic phase was isolated and the aqueous portion extracted twice with EtOAc. The organic phases were combined, dried over MgSO₄, filtered and concentrated to give 6.56g (41mmol) 3-(ethyloxy)-2,2-dimethyl-3-oxopropanoic acid as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ 4.20 (q, J=7.1Hz, 2H), 1.46(s, 6H), 1.26(t, J=7.1Hz, 3H).

Step 2: 400mg (2.50mmol) 3-(ethyloxy)-2,2-dimethyl-3-oxopropanoic acid dissolved in 4mL THF was treated with 1,1'-carbonyldiimidazole (405mg, 2.50mmol) at ambient temperature until CO₂ evolution ceased (~20min). To this solution was added 7.50mmol (3eq) of either ammonia, methylamine, ethylamine, 2-amino-2-methyl-1-propanol, cyclopropylamine, isopropylamine, 2-propen-1-ylamine, or N,N-dimethylamine. The reaction mixtures were shaken gently at ambient temperature for 16h, concentrated to dryness, partitioned between DCE (8mL) and 0.5N HCl (10mL), shaken vigorously, organic phases isolated, dried over MgSO₄ filtered and concentrated to dryness. Identity of these carboxamide ester intermediates was confirmed by ¹H NMR.

Step 3: The carboxamide esters so obtained were treated with 2.5mL (2.5mmol) of 1N LiOH in 2.5mL EtOH at ambient temperature for 16h. The reaction mixtures were concentrated to dryness and used in coupling reactions without further purification or characterization.



Method DD: Synthesis of carboxamide carboxylic acids from iodobenzoic acids or ester carboxylic acids (Acids 80-86) as exemplified by synthesis of 3-

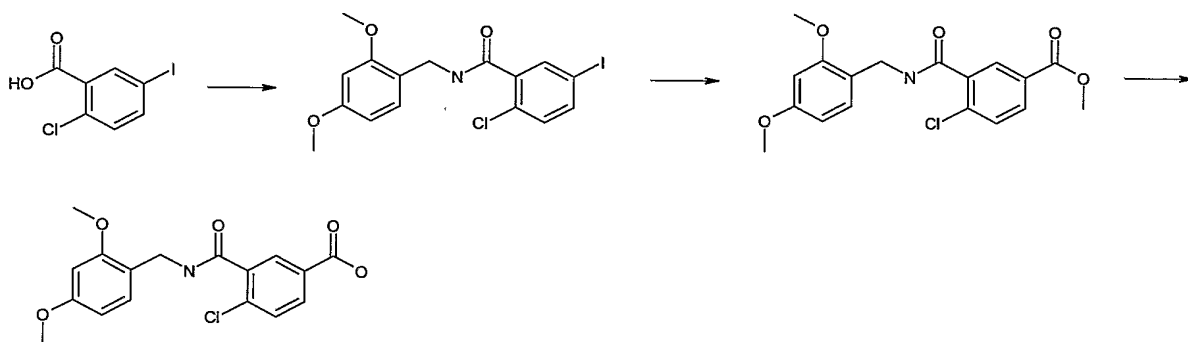
[(2,4-bis(methyloxy)phenyl)methyl]amino)carbonyl]-4-chlorobenzoic acid (Acid 84).

Step 1: 2-Chloro-5-iodobenzoic acid (2g, 7.08mmol) in 25mL THF was treated with 1,1'-carbonyldiimidazole (1.15g, 7.08mmol) at ambient temperature until CO₂ evolution ceased (~20min). 2,4-Dimethoxybenzylamine (1.18g, 7.08mmol) was added and stirred at ambient temperature for 16h. The reaction mixture was concentrated to dryness, partitioned between EtOAc and saturated NaHCO₃, the organic phase isolated, dried over MgSO₄, filtered and concentrated to give *N*-[(2,4-bis(methyloxy)phenyl)methyl]-2-chloro-5-iodobenzamide (3.00g, 6.95mmol) as a pale yellow oil that crystallized on standing. ¹H NMR (300 MHz, CDCl₃) δ 7.95(d, *J*=2.2Hz, 1H), 7.62(dd, *J*=8.5, 2.2Hz, 1H), 7.25(m, 1H), 7.10 (m, 1H), 6.63(m, 1H), 6.45 (m, 2H), 4.55(d, *J*=5.7 Hz, 2H), 3.83(s, 3H), 3.80(s, 3H). LCMS ES+ 431.82, 433.77 (M+H).

Step 2: *N*-[(2,4-bis(methyloxy)phenyl)methyl]-2-chloro-5-iodobenzamide (2.78g, 6.44mmol) dissolved in 100mL CH₃OH with dicyclohexylamine (3.85mL, 19mmol) was treated with POPd₂ catalyst (AC2000) under an atmosphere of CO(g) at 1atm pressure and ambient temperature for 3 days. The catalyst was filtered off and the filtrate concentrated to a small volume, cooled in ice bath, and the resultant precipitate filtered off. A second crop was obtained from the mother liquor and the two batches were combined to give methyl 3-[(2,4-bis(methyloxy)phenyl)methyl]amino)carbonyl]-4-chlorobenzoate (2.26g, 6.21mmol) as a white crystalline solid. ¹H NMR (300 MHz, DMSO-D₆) δ 8.82(m, 1H), 7.96(dd, *J*=8.3, 2.2Hz, 1H), 7.91(m, 1H), 7.65(d, *J*=8.3Hz, 1H), 7.19(d, *J*=8.2Hz, 1H), 6.56 (d, *J*=2.5Hz, 1H), 6.51(dd, *J*=8.3, 2.5Hz, 1H), 4.34(d, *J*=5.9Hz, 2H), 3.86(s, 3H), 3.79(s, 3H), 3.74(s, 3H). LCMS ES+ 363.99, 365.97(M+H).

Step 3: Methyl 3-[(2,4-bis(methyloxy)phenyl)methyl]amino)carbonyl]-4-chlorobenzoate (600mg, 1.65mmol) dissolved in 17mL CH₃OH was treated with 16.5mL 1N LiOH at ambient temperature for 16h. The reaction mixture was concentrated to dryness, partitioned between EtOAc and water, the aqueous phase isolated and the pH adjusted to 2 with 6N HCl. The resultant

precipitate was cooled in an ice bath with stirring, filtered, and washed with water to give 3-[(2,4-bis(methoxy)phenyl)methyl]amino)carbonyl]-4-chlorobenzoic acid (533mg, 1.52mmol) as a white crystalline solid. ¹H NMR (300 MHz, DMSO-D₆) δ ppm 8.96(m, 1H), 8.29(d, *J*=2.2 Hz, 1 H), 8.00(dd, *J*=8.4, 2.3 Hz, 1 H), 7.65(d, *J*=8.3 Hz, 1 H), 7.09(d, *J*=8.3 Hz, 1 H), 6.55(d, *J*=2.3 Hz, 1 H), 6.50(dd, *J*=8.3, 2.3 Hz, 1 H), 4.35(d, *J*=5.6 Hz, 1 H), 3.79(s, 3H), 3.73(s, 3H). LCMS ES+ 349.88, 351.91 (M+H).

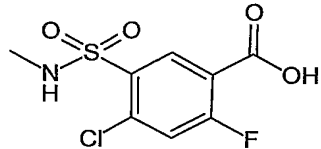
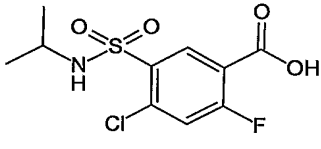
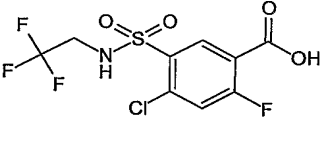
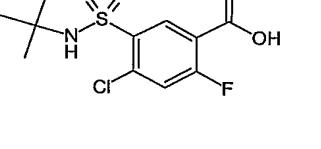
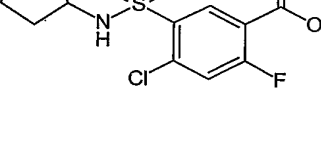
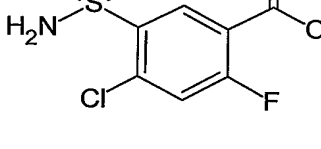
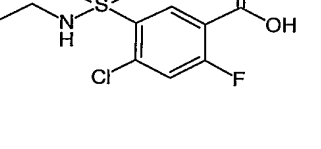
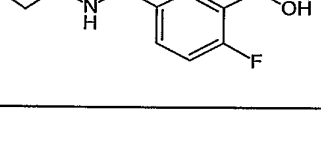


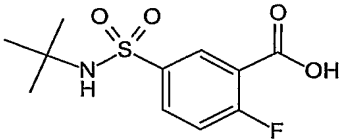
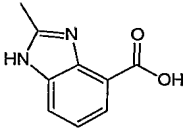
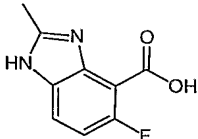
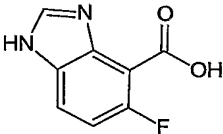
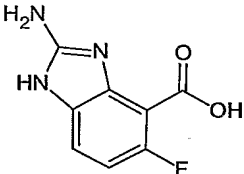
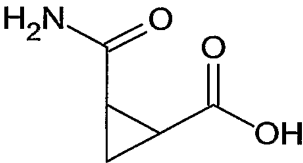
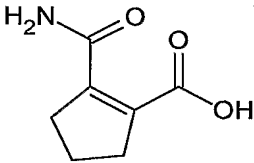
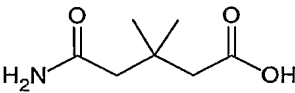
Acids 80-83 were synthesized in an analogous fashion from the appropriately substituted iodobenzoic acid and the appropriate amine.

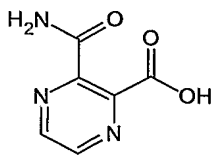
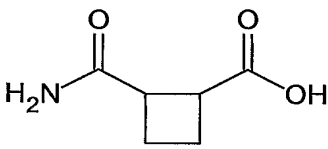
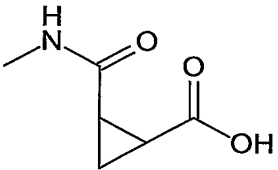
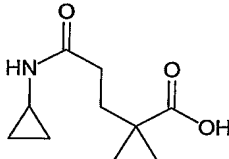
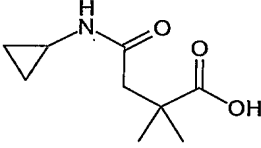
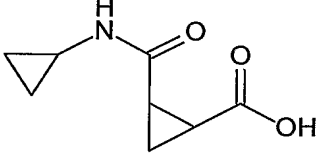
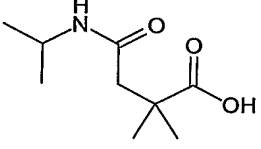
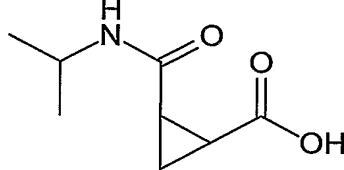
Acids 85, 86, and 154 were synthesized from diethyl dimethylpropanedioate, diethyl diethylpropanedioate, or diethyl 1,1-cyclobutanedicarboxylate, respectively, and 2,4-Dimethoxybenzylamine using Method CC, step 1 and Method DD steps 1 and 3.

The table below lists acids 55-154, their properties, method of their synthesis as well as yields.

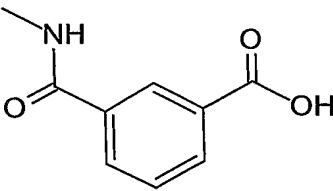
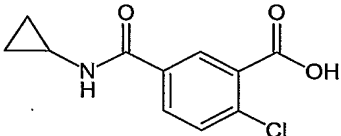
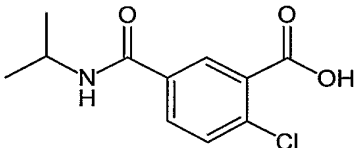
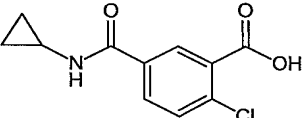
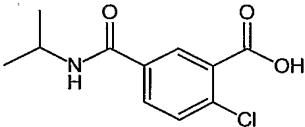
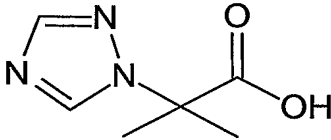
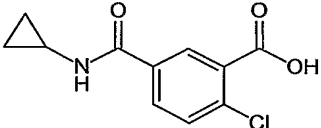
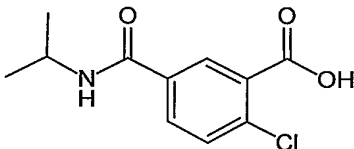
Acid #	Structure	Yield	ES-LCMS	Ion	Method
Acid 55			293.94	(M+H)	H

Acid 56		75	267.95	(M+H)	H
Acid 57		57	317.96	(M+Na)	H
Acid 58		85	357.92	(M+Na)	H
Acid 59		23	332	(M+Na)	H
Acid 60		77	343.97	(M+Na)	H
Acid 61		55	275.87	(M+Na)	H
Acid 62			282.08	(M+H)	H
Acid 63			310.01	(M+Na)	H

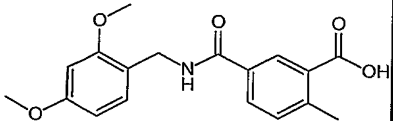
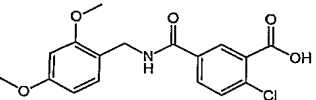
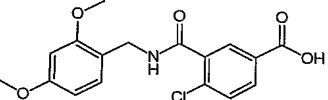
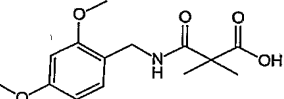
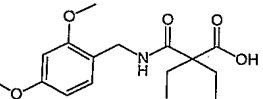
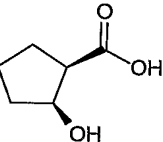
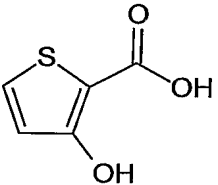
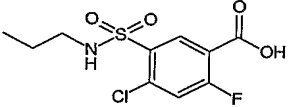
Acid 64			298.1	(M+Na)	H
Acid 65					BB
Acid 66					BB
Acid 67					BB
Acid 68					BB
Acid 69					AA
Acid 70					AA
Acid 71					AA

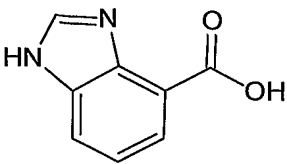
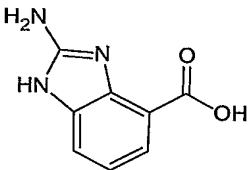
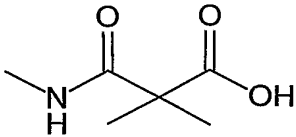
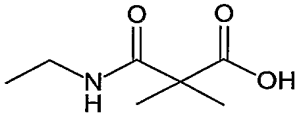
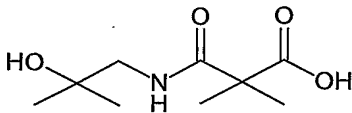
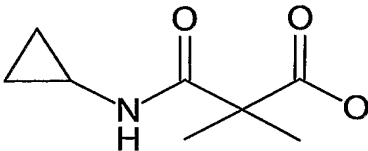
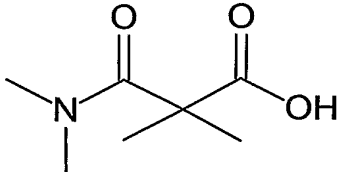
Acid 72					AA
Acid 73					AA
Acid 74					AA
Acid 75					AA
Acid 76					AA
Acid 77					AA
Acid 78					AA
Acid 79					AA

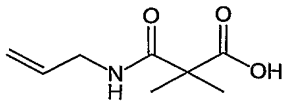
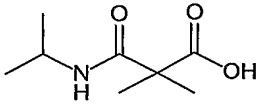
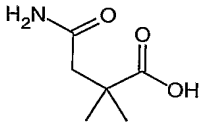
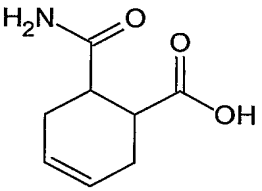
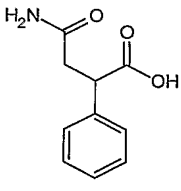
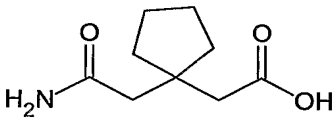
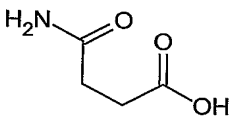
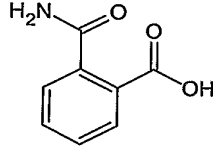
743

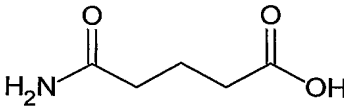
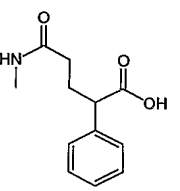
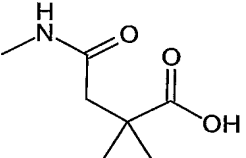
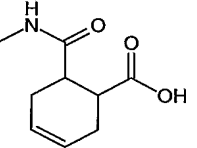
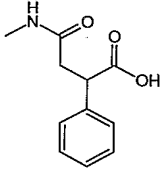
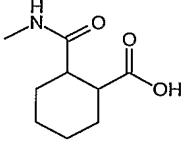
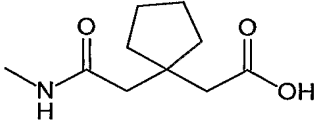
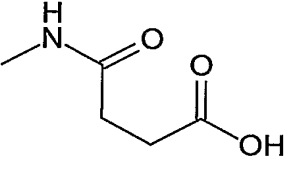
glax					
Acid 80		68	239.9	(M+H)	DD
Acid 81		73	241.91	(M+H)	DD
Acid 80		68	239.9	(M+H)	DD
Acid 81		73	241.91	(M+H)	DD
comm ercial					
Acid 80		68	239.9	(M+H)	DD
Acid 81		73	241.91	(M+H)	DD

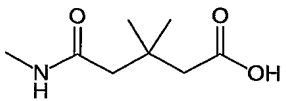
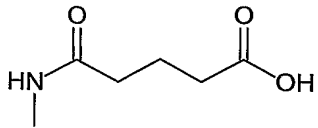
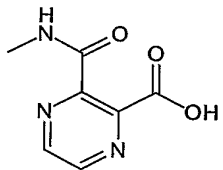
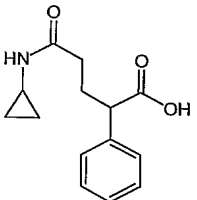
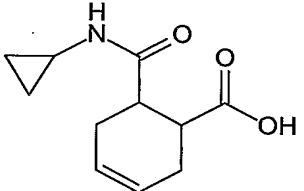
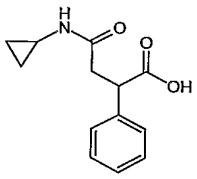
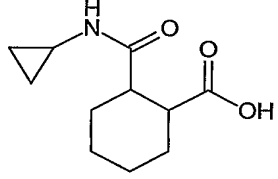
744

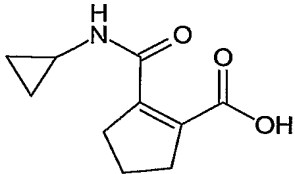
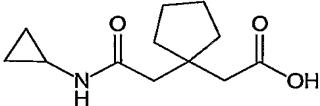
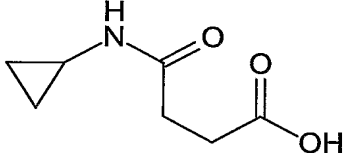
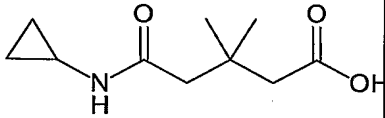
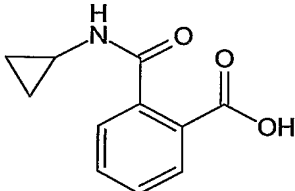
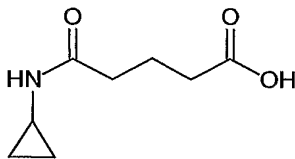
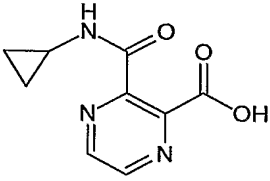
Acid 82		54	329.95	(M+H)	DD
Acid 83		94	349.89, 351.91	(M+H)	DD
Acid 84		92	349.88, 351.91	(M+H)	DD
Acid 85		100	304	(M+Na)	DD
Acid 86		82	331.98	(M+Na)	DD
comm ercial					
glax					
Acid 87		75	318.03	(M+Na)	H

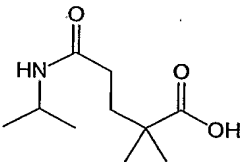
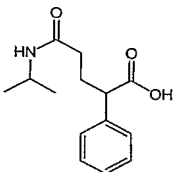
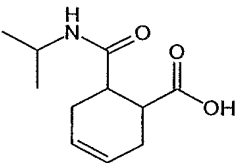
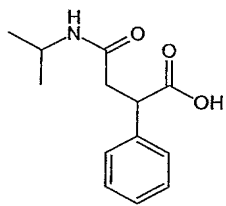
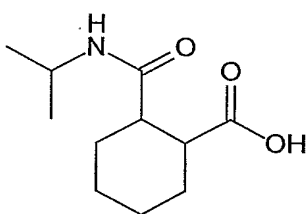
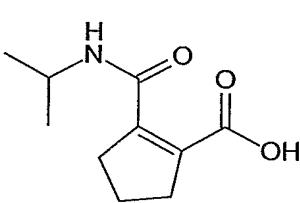
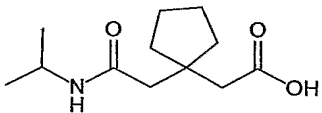
Acid 88					BB
Acid 89					BB
Acid 90					CC
Acid 91					CC
Acid 92					CC
Acid 93					CC
Acid 94					CC

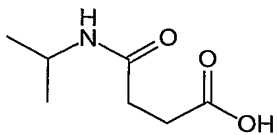
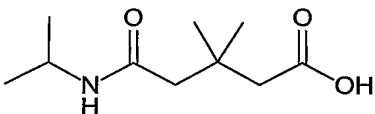
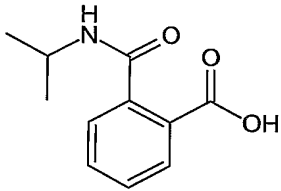
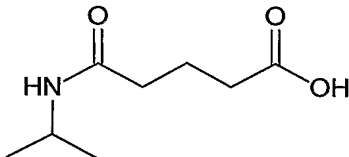
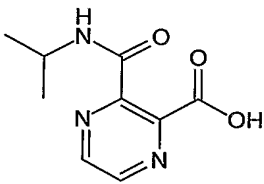
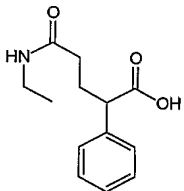
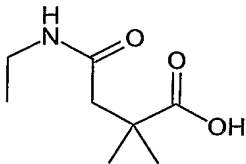
Acid 95					CC
Acid 96					CC
Acid 97					AA
Acid 98					AA
Acid 99					AA
Acid 100					AA
Acid 101					AA
Acid 102					AA

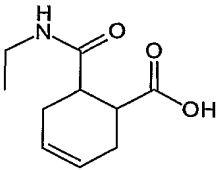
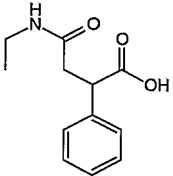
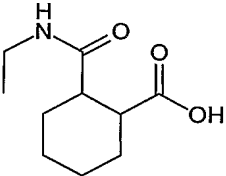
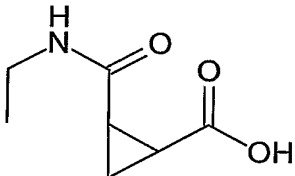
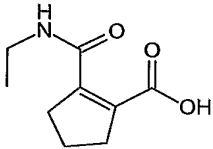
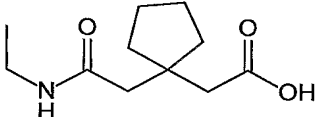
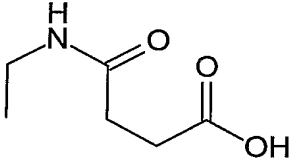
Acid 103					AA
Acid 104					AA
Acid 105					AA
Acid 106					AA
Acid 107					AA
Acid 108					AA
Acid 109					AA
Acid 110					AA

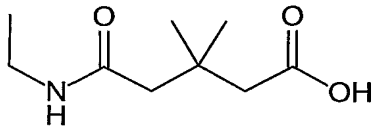
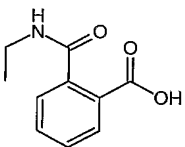
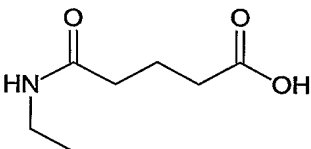
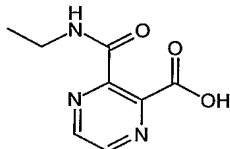
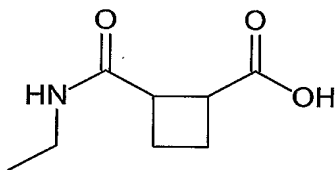
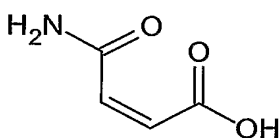
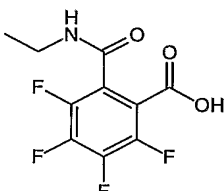
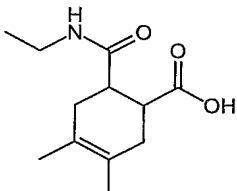
Acid 111					AA
Acid 112					AA
Acid 113					AA
Acid 114					AA
Acid 115					AA
Acid 116					AA
Acid 117					AA

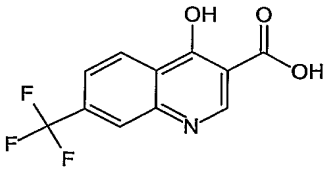
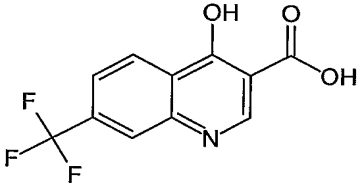
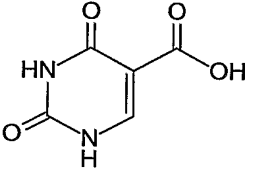
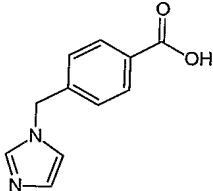
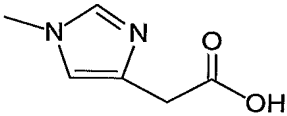
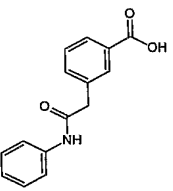
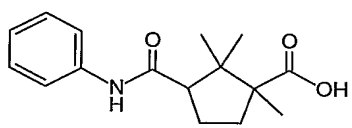
Acid 118					AA
Acid 119					AA
Acid 120					AA
Acid 121					AA
Acid 122					AA
Acid 123					AA
Acid 124					AA

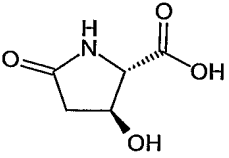
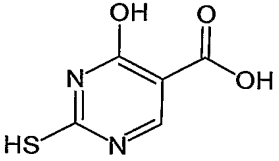
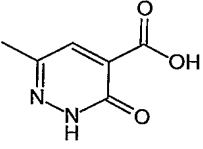
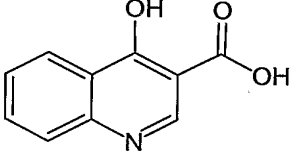
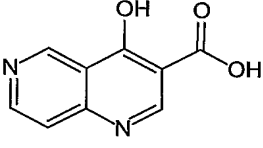
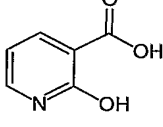
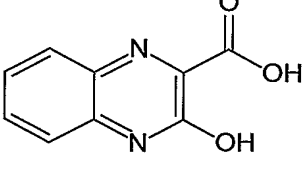
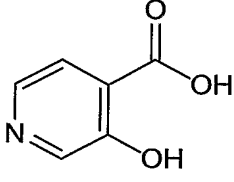
Acid 125					AA
Acid 126					AA
Acid 127					AA
Acid 128					AA
Acid 129					AA
Acid 130					AA
Acid 131					AA

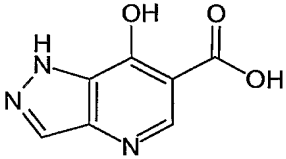
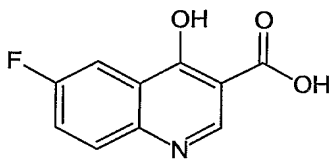
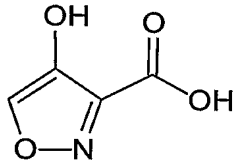
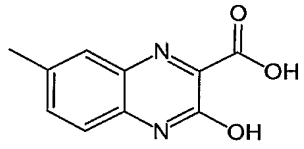
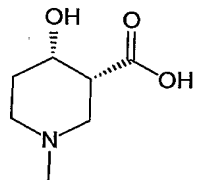
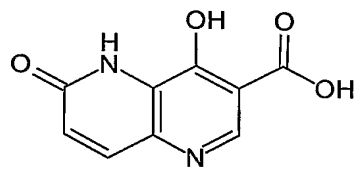
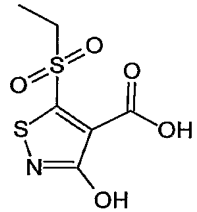
Acid 132					AA
Acid 133					AA
Acid 134					AA
Acid 135					AA
Acid 136					AA
Acid 137					AA
Acid 138					AA

Acid 139					AA
Acid 140					AA
Acid 141					AA
Acid 142					AA
Acid 143					AA
Acid 144					AA
Acid 145					AA

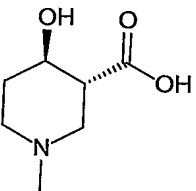
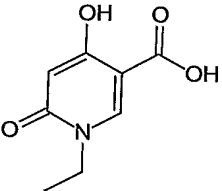
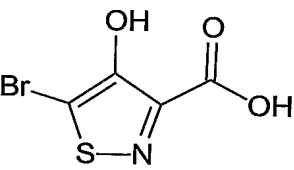
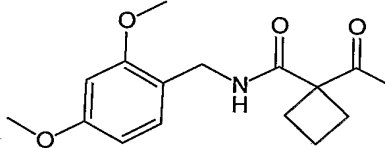
Acid 146					AA
Acid 147					AA
Acid 148					AA
Acid 149					AA
Acid 150					AA
Acid 151					AA
Acid 152					AA
Acid 153					AA

glax	 <chem>OC(=O)c1cnc2cc(C(F)(F)F)ccc2o1</chem>				
glax	 <chem>OC(=O)c1cnc2cc(C(F)(F)F)ccc2o1</chem>				
glax	 <chem>OC(=O)c1c[nH]c(=O)[nH]c1=O</chem>				
glax	 <chem>OC(=O)c1ccc(cc1)CN2C=NC=C2</chem>				
glax	 <chem>OC(=O)CN1C=CN1C</chem>				
glax	 <chem>OC(=O)c1ccc(cc1)CC(=O)Nc2ccccc2</chem>				
glax	 <chem>OC(=O)C1(C)CCCC1C(=O)Nc2ccccc2</chem>				

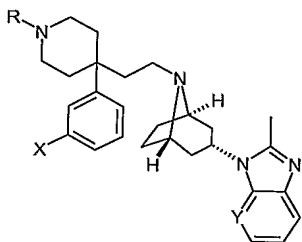
glax	 <chem>O=C1CC[C@H](C(=O)O)N1</chem>				
glax	 <chem>OS1=NC=C(C(=O)O)N=C1S</chem>				
glax	 <chem>CC1=CN(C(=O)O)C(=O)NC1=O</chem>				
glax	 <chem>O=C1C=C2C(=C1)C=CC=CC2C(=O)O</chem>				
glax	 <chem>O=C1C=CC2=CC=CC=C2C(=O)O1</chem>				
glax	 <chem>O=C1C=CC2=CC=CC=C2C(=O)O1</chem>				
glax	 <chem>O=C1C=CC2=CC=CC=C2C(=O)O1</chem>				
glax	 <chem>O=C1C=CC2=CC=CC=C2C(=O)O1</chem>				

glax	 <chem>O=C(O)c1cc2c(c1)c[nH]2</chem>				
glax	 <chem>O=C(O)c1cc2cc(F)ccc2n1</chem>				
glax	 <chem>O=C(O)c1ccoc1</chem>				
glax	 <chem>O=C(O)c1nc2cc(C)ccc2n1</chem>				
glax	 <chem>O=C(O)[C@H]1CCN(C)CC1O</chem>				
glax	 <chem>O=C(O)c1cc2c(c1)c(=O)[nH]2</chem>				
glax	 <chem>O=C(O)c1c(O)[nH]s1</chem>				

757

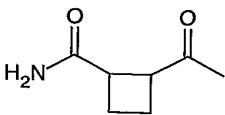
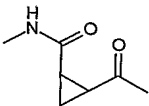
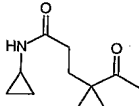
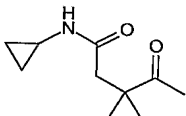
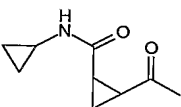
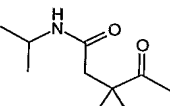
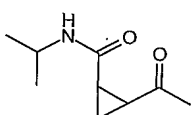
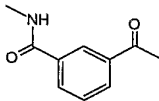
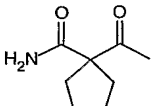
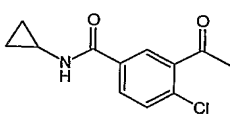
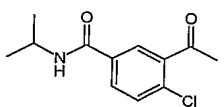
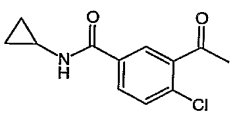
glax					
glax					
glax					
Acid 154		83	315.94	(M+Na)	DD

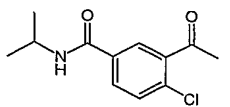
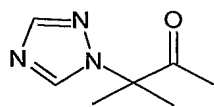
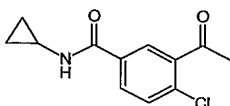
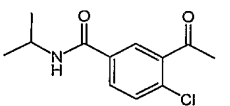
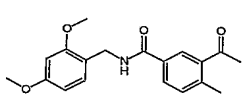
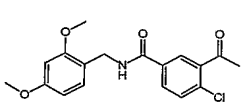
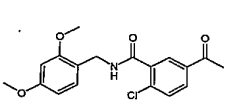
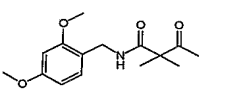
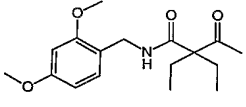
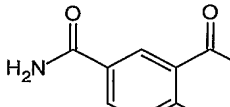
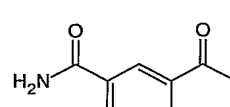
The following examples were prepared using acids described elsewhere in this invention

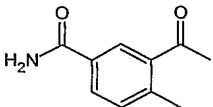
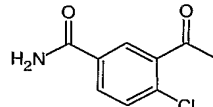
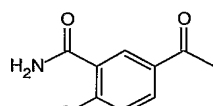
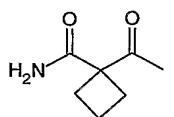
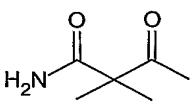
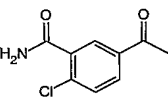
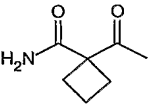
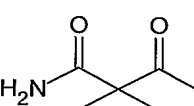
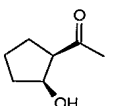
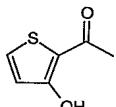
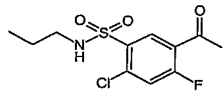


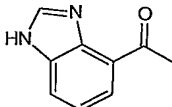
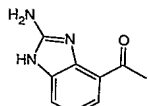
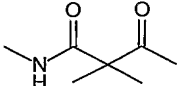
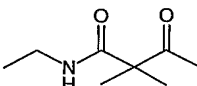
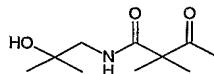
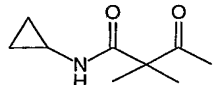
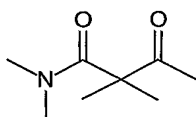
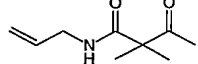
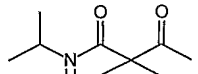
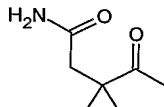
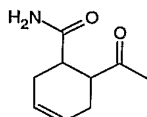
Example	Acid # or source	R	X	Y	% Yield	LCMS ES	Ion	Method
1021	Acid 83		H	C	36	610.18	(M+H)	F
1022	Acid 82		CH 3	C	52	604.24	(M+H)	F
1023	Acid 83		CH 3	C	52	624.22	(M+H)	F
1024	Acid 85		CH 3	C	38	556.27	(M+H)	F
1025	Acid 55		F	C	42	722.36	(M+H)	A
1026	Acid 56		F	C	36	696.18	(M+H)	A
1027	Acid 57		F	C	52	724.38	(M+H)	A
1028	Acid 58		F	C	56	764.33	(M+H)	A
1029	Acid 59		F	C	32	738.37	(M+H)	A
1030	Acid 60		F	C	50	750.23	(M+H)	A
1031	Acid 61		F	C	49	682.32	(M+H)	A

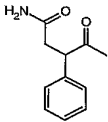
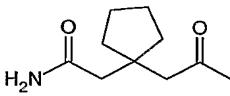
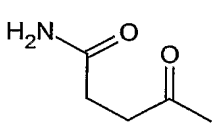
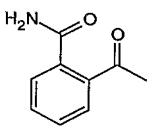
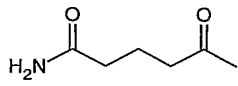
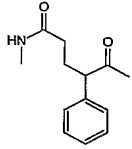
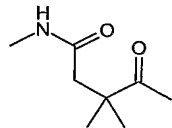
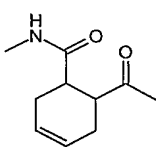
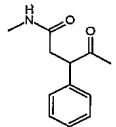
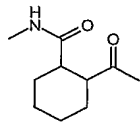
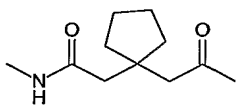
1032	Acid 62		F	C	54	710.34	(M+H)	A
1033	Acid 63		F	C	26	716.42	(M+H)	A
1034	Acid 64		F	C	29	704.42	(M+H)	A
1035	Acid 65		F	C	28	605.35	(M+H)	A
1036	Acid 66		F	C	48	623.32	(M+H)	A
1037	Acid 67		F	C	46	609.28	(M+H)	A
1038	Acid 68		F	C	13	624.34	(M+H)	A
1039	Acid 69		F	C	44	558.38	(M+H)	A
1040	Acid 70		F	C	57	584.39	(M+H)	A
1041	Acid 71		F	C	58	588.45	(M+H)	A
1042	Acid 72		F	C	52	596.35	(M+H)	A

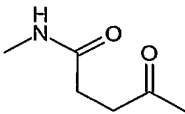
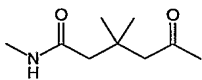
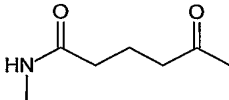
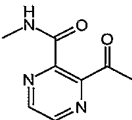
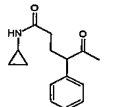
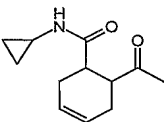
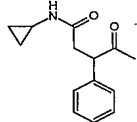
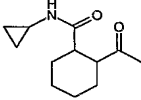
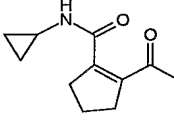
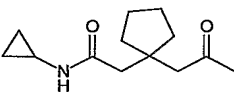
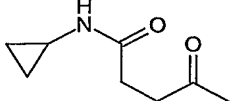
1043	Acid 73		F	C	23	572.34	(M+H)	A
1044	Acid 74		F	C	41	572.35	(M+H)	A
1045	Acid 75		F	C	29	628.39	(M+H)	A
1046	Acid 76		F	C	43	614.42	(M+H)	A
1047	Acid 77		F	C	64	598.42	(M+H)	A
1048	Acid 78		F	C	27	616.5	(M+H)	A
1049	Acid 79		F	C	39	600.45	(M+H)	A
1050	glax		F	C	37	608.4	(M+H)	A
1051	Acid 86		F	C	37	588.4	(M+H)	A
1052	Acid 80		H	C	48	650.19	(M+H)	A
1053	Acid 81		H	C	39	652.22	(M+H)	A
1054	Acid 80		F	C	56	668.22	(M+H)	A

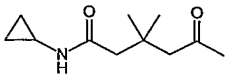
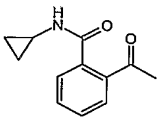
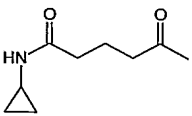
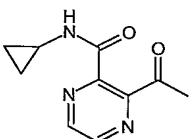
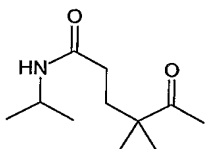
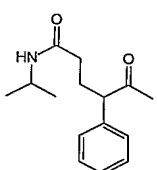
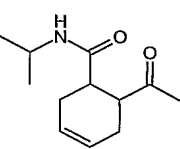
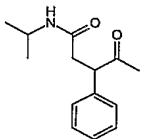
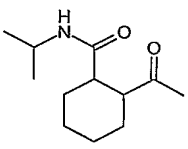
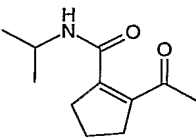
1055	Acid 81		F	C	43	670.21	(M+H)	A
1056	commercial		F	C	39	584.24	(M+H)	A
1057	Acid 80		CH 3	C	41	664.25	(M+H)	A
1058	Acid 81		CH 3	C	41	666.26	(M+H)	A
1059	Acid 82		F	C	45	758.33	(M+H)	A
1060	Acid 83		F	C	36	778.29	(M+H)	A
1061	Acid 84		F	C	66	778.29	(M+H)	A
1062	Acid 85		F	C	41	710.28	(M+H)	A
1063	Acid 86		F	C	56	738.33	(M+H)	A
1064	Acid 82		H	C	39	590.25	(M+H)	F
1065	Acid 84		H	C	13	610.18	(M+H)	F

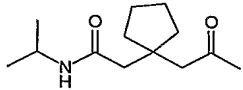
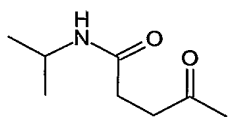
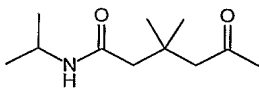
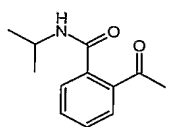
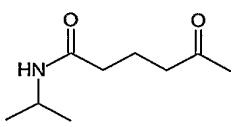
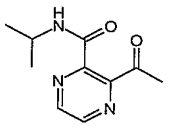
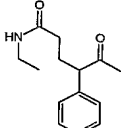
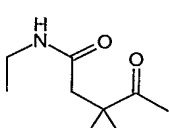
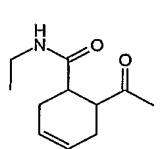
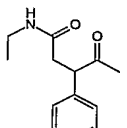
1066	Acid 82		F	C	48	608.24	(M+H)	F
1067	Acid 83		F	C	53	628.18	(M+H)	F
1068	Acid 84		F	C	47	628.17	(M+H)	F
1069	Acid 154		F	C	46	572.27	(M+H)	F
1070	Acid 85		F	C	33	560.26	(M+H)	F
1071	Acid 84		CH 3	C	23	624.24	(M+H)	F
1072	Acid 154		CH 3	C	34	568.28	(M+H)	F
1073	Acid 85		H	C	18	542.29	(M+H)	F
1075	comm ercial		F	C	49	559.14	(M+H)	A
1076	glax		F	C	39	573.05	(M+H)	A
1077	Acid 87		F	C	52	724.38	(M+H)	A

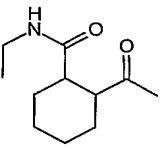
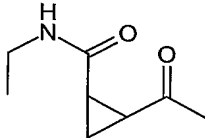
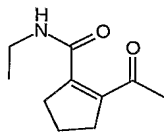
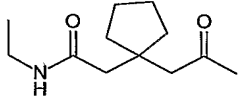
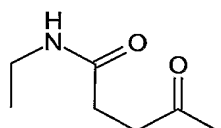
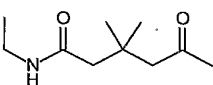
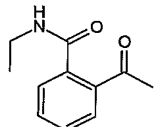
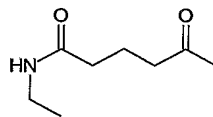
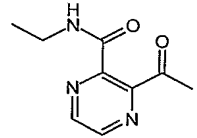
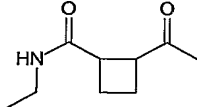
1078	Acid 88		F	C	27	591.27	(M+H)	A
1079	Acid 89		F	C	22	606.35	(M+H)	A
1080	Acid 90		F	C	24	574.35	(M+H)	A
1081	Acid 91		F	C	34	588.36	(M+H)	A
1082	Acid 92		F	C	23	632.47	(M+H)	A
1083	Acid 93		F	C	33	598.79	(M-1)	A
1084	Acid 94		F	C	18	588.33	(M+H)	A
1085	Acid 95		F	C	41	600.37	(M+H)	A
1086	Acid 96		F	C	45	602.4	(M+H)	A
1087	Acid 97		F	C	33	574.36	(M+H)	A
1088	Acid 98		F	C	32	598.39	(M+H)	A

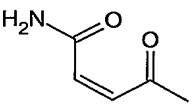
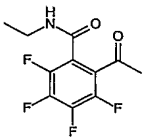
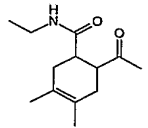
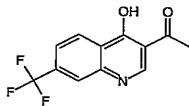
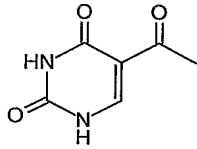
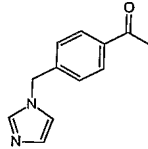
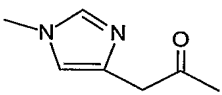
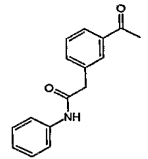
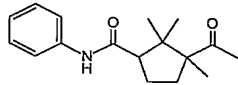
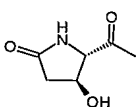
1089	Acid 99		F	C	49	622.42	(M+H)	A
1090	Acid 100		F	C	55	614.44	(M+H)	A
1091	Acid 101		F	C	50	546.36	(M+H)	A
1092	Acid 102		F	C	15	594.37	(M+H)	A
1093	Acid 103		F	C	54	560.41	(M+H)	A
1094	Acid 104		F	C	27	650.43	(M+H)	A
1095	Acid 105		F	C	40	610.32	(M+H)	A
1096	Acid 106		F	C	42	612.35	(M+H)	A
1097	Acid 107		F	C	27	636.39	(M+H)	A
1098	Acid 108		F	C	31	614.39	(M+H)	A
1099	Acid 109		F	C	31	628.44	(M+H)	A

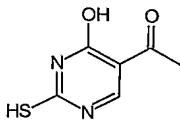
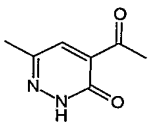
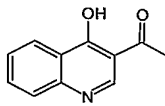
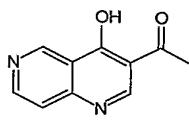
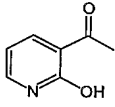
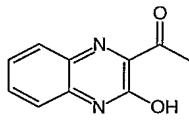
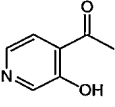
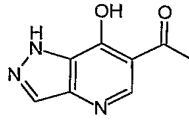
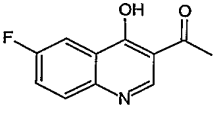
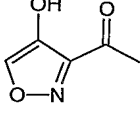
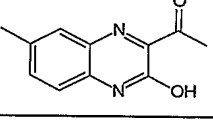
1100	Acid 110		F	C	34	560.37	(M+H)	A
1101	Acid 111		F	C	40	602.38	(M+H)	A
1102	Acid 112		F	C	39	574.4	(M+H)	A
1103	Acid 113		F	C	34	610.35	(M+H)	A
1104	Acid 114		F	C	20	676.4	(M+H)	A
1105	Acid 115		F	C	31	638.38	(M+H)	A
1106	Acid 116		F	C	27	662.42	(M+H)	A
1107	Acid 117		F	C	25	640.49	(M+H)	A
1108	Acid 118		F	C	37	624.44	(M+H)	A
1109	Acid 119		F	C	19	654.44	(M+H)	A
1110	Acid 120		F	C	53	586.41	(M+H)	A

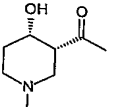
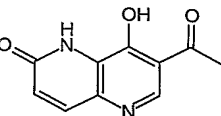
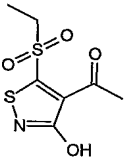
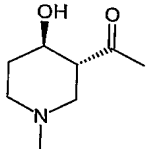
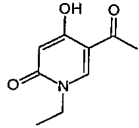
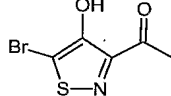
1111	Acid 121		F	C	29	628.44	(M+H)	A
1112	Acid 122		F	C	41	634.42	(M+H)	A
1113	Acid 123		F	C	47	600.45	(M+H)	A
1114	Acid 124		F	C	31	636.36	(M+H)	A
1115	Acid 125		F	C	21	630.43	(M+H)	A
1116	Acid 126		F	C	24	678.51	(M+H)	A
1117	Acid 127		F	C	38	640.51	(M+H)	A
1118	Acid 128		F	C	33	664.5	(M+H)	A
1119	Acid 129		F	C	35	642.51	(M+H)	A
1120	Acid 130		F	C	38	626.47	(M+H)	A

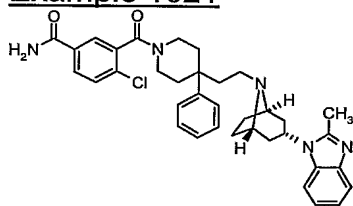
1121	Acid 131		F	C	15	656.49	(M+H)	A
1122	Acid 132		F	C	34	588.45	(M+H)	A
1123	Acid 133		F	C	36	630.51	(M+H)	A
1124	Acid 134		F	C	33	636.45	(M+H)	A
1125	Acid 135		F	C	34	602.48	(M+H)	A
1126	Acid 136		F	C	29	638.43	(M+H)	A
1127	Acid 137		F	C	20	664.52	(M+H)	A
1128	Acid 138		F	C	25	602.45	(M+H)	A
1129	Acid 139		F	C	26	626.45	(M+H)	A
1130	Acid 140		F	C	31	650.51	(M+H)	A

1131	Acid 141		F	C	25	628.52	(M+H)	A
1132	Acid 142		F	C	44	586.42	(M+H)	A
1133	Acid 143		F	C	34	612.49	(M+H)	A
1134	Acid 144		F	C	18	640.49	(M+H)	A
1135	Acid 145		F	C	41	574.43	(M+H)	A
1136	Acid 146		F	C	23	616.48	(M+H)	A
1137	Acid 147		F	C	25	622.44	(M+H)	A
1138	Acid 148		F	C	37	588.45	(M+H)	A
1139	Acid 149		F	C	35	624.44	(M+H)	A
1140	Acid 150		F	C	35	600.46	(M+H)	A

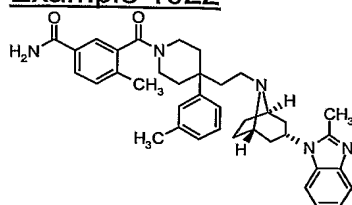
1141	Acid 151		F	C	33	544.35	(M+H)	A
1142	Acid 152		F	C	15	694.34	(M+H)	A
1143	Acid 153		F	C	14	654.43	(M+H)	A
1144	glax		F	C	52	686.4	(M+H)	A
1145	glax		F	C	18	585.34	(M+H)	A
1146	glax		F	C	29	631.37	(M+H)	A
1147	glax		F	C	30	569.35	(M+H)	A
1148	glax		F	C	30	684.4	(M+H)	A
1149	glax		F	C	12	704.44	(M+H)	A
1150	glax		F	C	11	574.41	(M+H)	A

1151	glax		F	C	45	601.36	(M+H)	A
1152	glax		F	C	65	583.38	(M+H)	A
1153	glax		F	C	47	618.41	(M+H)	A
1154	glax		F	C	17	619.39	(M+H)	A
1155	glax		F	C	54	568.38	(M+H)	A
1156	glax		F	C	63	619.4	(M+H)	A
1157	glax		F	C	44	568.37	(M+H)	A
1158	glax		F	C	15	608.43	(M+H)	A
1159	glax		F	C	38	636.4	(M+H)	A
1160	glax		F	C	13	558.36	(M+H)	A
1161	glax		F	C	76	633.43	(M+H)	A

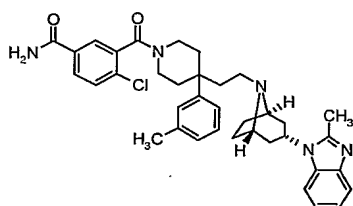
1162	glax		F	C	47	588.45	(M+H)	A
1163	glax		F	C	12	635.45	(M+H)	A
1164	glax		F	C	23	666.36	(M+H)	A
1165	glax		F	C	70	588.45	(M+H)	A
1166	glax		F	C	41	612.41	(M+H)	A
1167	glax		F	C	20	652.26	(M+H)	A

Example 1021

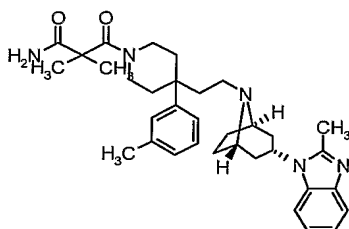
4-chloro-3-[(4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-phenylpiperidin-1-yl)carbonyl]benzamide. ^1H NMR (300 MHz, CD_3OD) δ 7.96-7.07(m, 12H), 4.75(m, 1H), 4.21 (m, 1H), 3.90-3.10(m, 6H), 2.53 (s, 3H), 2.50-1.68 (m, 15H).

Example 1022

4-methyl-3-[[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl)-1-piperidinyl]carbonyl]benzamide. ^1H NMR (300 MHz, CD_3OD) δ 7.96-7.07(m, 11H), 4.75(m, 1H), 4.31-4.15(m, 1H), 3.91-3.10(m, 6H), 2.53 (s, 3H), 2.50-1.68 (m, 15H), 2.43(s, 1.5H), 2.38 (s, 3H), 2.25(s, 1.5H).

Example 1023

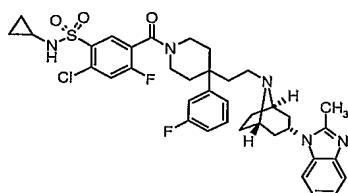
4-chloro-3-[[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl)-1-piperidinyl]carbonyl]benzamide. ^1H NMR (300 MHz, CD_3OD) δ 7.96-7.07(m, 11H), 4.75(m, 1H), 4.22 (m, 1H), 3.80-3.16(m, 6H), 2.53 (s, 3H), 2.50-1.68 (m, 15H), 2.38 (s, 3H).

Example 1024

2,2-dimethyl-3-[4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-4-(3-methylphenyl)-1-piperidinyl]-3-azabicyclo[3.2.1]oct-8-yl]ethyl]benzamide.

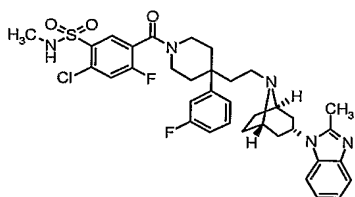
oxopropanamide. ^1H NMR (300 MHz, CD_3OD) δ 7.55-7.06(m, 8H), 4.77(m, 1H), 4.02 (m, 1H), 3.89-3.17(m, 6H), 2.67-1.68 (m, 21H), 2.56 (s, 3H), 2.37 (s, 3H).

Example 1025

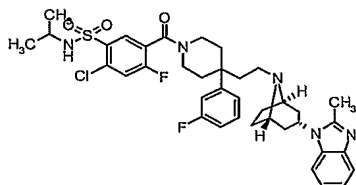


2-chloro-N-cyclopropyl-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide. ^1H NMR (300 MHz, CD_3OD) δ ppm 8.18(m, 1H), 7.67(d, $J=8.8\text{Hz}$, 1H), 7.58(m, 1H), 7.47(m, 2H), 7.30(s, 1H), 7.29-7.20(m, 3H), 7.05(m, 1H), 4.79(m, 1H), 4.21(m, 1H), 3.60-3.25(m, 8H), 2.59(s, 3H), 2.52-1.70(m, 15H), 0.56(m, 4H).

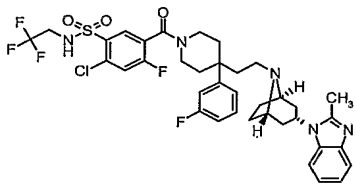
Example 1026



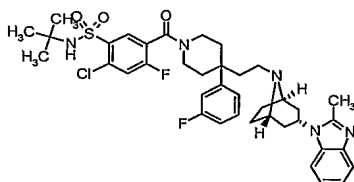
2-chloro-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzenesulfonamide. ^1H NMR (300 MHz, CD_3OD) δ ppm 8.09(m, 1H), 7.60(d, $J=8.8\text{Hz}$, 1H), 7.53(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.75(m, 1H), 4.16(m, 1H), 3.53-3.18(m, 8H), 2.55(d, $J=9.3\text{Hz}$, 3H), 2.52-1.70(m, 16H).

Example 1027

2-chloro-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-(1-methylethyl)benzenesulfonamide. ^1H NMR (300 MHz, CD_3OD) δ ppm 8.11(m, 1H), 7.60(d, $J=8.8\text{Hz}$, 1H), 7.53(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.74(m, 1H), 4.17(m, 1H), 3.53-3.18(m, 8H), 2.53(s, 3H), 2.52-1.70(m, 14H), 1.07 (d, $J=6.5\text{Hz}$, 6H).

Example 1028

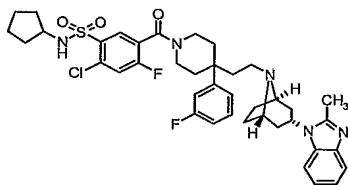
2-chloro-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-(2,2,2-trifluoroethyl)benzenesulfonamide. ^1H NMR (300 MHz, CD_3OD) δ ppm 8.10(m, 1H), 7.60(d, $J=8.8\text{Hz}$, 1H), 7.51(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.73(m, 1H), 4.16(m, 1H), 3.77 (q, $J=9.4\text{ Hz}$, 2 H), 3.53-3.18(m, 8H), 2.53(s, 3H), 2.52-1.68(m, 13H).

Example 1029

2-chloro-N-(1,1-dimethylethyl)-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-

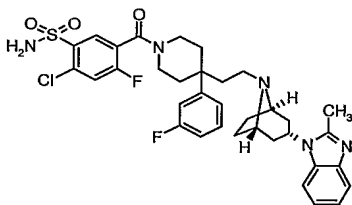
piperidinyl)carbonyl]benzenesulfonamide. ^1H NMR (300 MHz, CD_3OD) δ ppm 8.10(m, 1H), 7.58(d, $J=8.8\text{Hz}$, 1H), 7.51(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.74(m, 1H), 4.17(m, 1H), 3.53-3.18(m, 8H), 2.53(s, 3H), 2.52-1.69(m, 13H), 1.20(s, 9H).

Example 1030



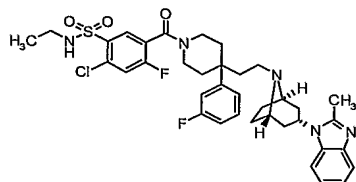
2-chloro-N-cyclopentyl-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide. ^1H NMR (300 MHz, CD_3OD) δ ppm 8.11(m, 1H), 7.60(d, $J=8.8\text{Hz}$, 1H), 7.51(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.72(m, 1H), 4.16(m, 1H), 3.57-3.18(m, 8H), 2.53(s, 3H), 2.52-1.39(m, 22H).

Example 1031



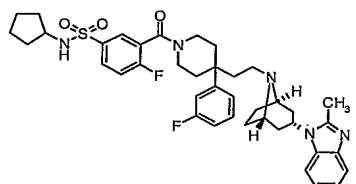
2-chloro-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide. ^1H NMR (300 MHz, CD_3OD) δ ppm 8.10(m, 1H), 7.58(d, $J=9.0\text{Hz}$, 1H), 7.51(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.73(m, 1H), 4.16(m, 1H), 3.52-3.19(m, 8H), 2.53(s, 3H), 2.52-1.69(m, 13H).

Example 1032



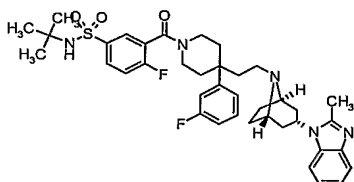
2-chloro-N-ethyl-4-fluoro-5-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide. ^1H NMR (300 MHz, CD_3OD) \square ppm 8.09(m, 1H), 7.59(d, $J=9.1\text{Hz}$, 1H), 7.51(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.74(m, 1H), 4.16(m, 1H), 3.52-3.19(m, 8H), 2.97(q, $J=7.2\text{Hz}$, 2H), 2.53(s, 3H), 2.52-1.69(m, 13H), 1.06(t, $J=7.2\text{Hz}$, 3H).

Example 1033



N-cyclopentyl-4-fluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide. ^1H NMR (300 MHz, CD_3OD) \square ppm 7.98(m, 1H), 7.88(m, 1H), 7.53(m, 1H), 7.41(m, 3H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.73(m, 1H), 4.17(m, 1H), 3.60-3.18(m, 8H), 2.52(s, 3H), 2.52-1.34(m, 22H).

Example 1034

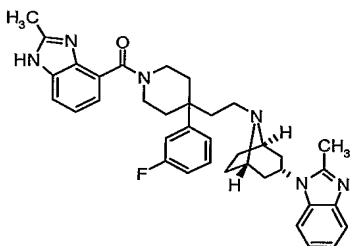


N-(1,1-dimethylethyl)-4-fluoro-3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzenesulfonamide.

777

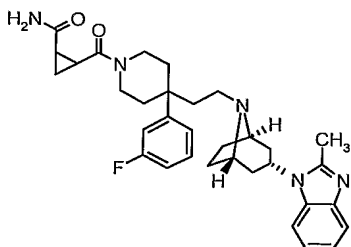
piperidiny]carbonyl]benzenesulfonamide. ^1H NMR (300 MHz, CD_3OD) δ ppm 8.01(m, 1H), 7.89(m, 1H), 7.52(m, 1H), 7.40(m, 3H), 7.25-7.16(m, 4H), 7.00(m, 1H), 4.74(m, 1H), 4.17(m, 1H), 3.52-3.17(m, 8H), 2.53(s, 3H), 2.52-1.68(m, 13H), 1.19(s, 9H).

Example 1035

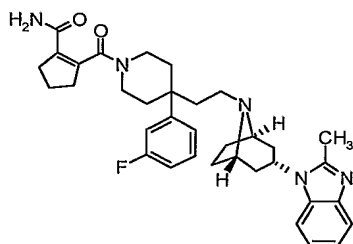


1-[(1R,5S)-8-(2-{4-(3-fluorophenyl)-1-[(2-methyl-1H-benzimidazol-4-yl)carbonyl]-4-piperidiny]ethyl)-8-azabicyclo[3.2.1]oct-3-yl]-2-methyl-1H-benzimidazole. ^1H NMR (300 MHz, CD_3OD) δ ppm 8.01-6.94(m, 11H), 4.90-4.72(m, 1H), 3.97(m, 1H), 3.70-3.16(m, 8H), 2.65(s, 3H), 2.55(s, 3H), 2.46-1.38(m, 14H).

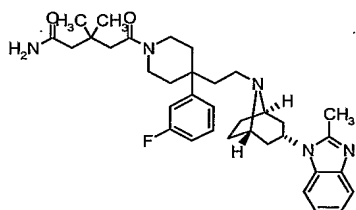
Example 1039



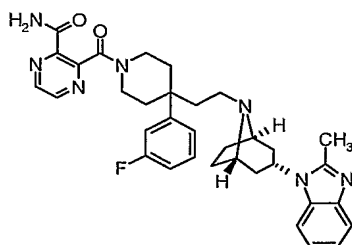
2-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]cyclopropanecarboxamide. ^1H NMR (300 MHz, CD_3OD) δ ppm 7.53(m, 1H), 7.40(m, 2H), 7.25-7.14(m, 4H), 6.98(m, 1H), 4.74(m, 1H), 4.11-3.79(m, 2H), 3.52-3.29(m, 7H), 3.08(m, 1H), 2.55(s, 3H), 2.52-1.17(m, 16H).

Example 1040

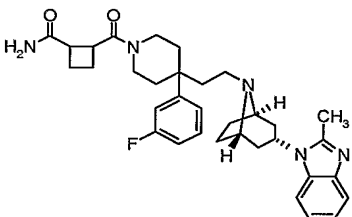
2-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]-1-cyclopentene-1-carboxamide. ^1H NMR (300 MHz, CD_3OD) \square ppm 7.53(m, 1H), 7.41(m, 2H), 7.25-7.14(m, 4H), 6.97(m, 1H), 4.74(m, 1H), 4.0(m, 1H), 3.55(m, 1H), 3.35-3.20(m, 5H), 3.00(m, 1H), 2.54(s, 3H), 2.80-1.17(m, 20H).

Example 1041

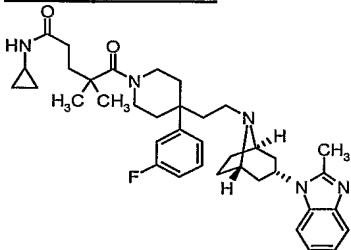
5-(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]-3,3-dimethyl-5-oxopentanamide. ^1H NMR (300 MHz, CD_3OD) \square ppm 7.50(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 6.98(m, 1H), 4.74(m, 1H), 4.00(m, 1H), 3.83(m, 1H), 3.42-1.68(m, 24H), 2.55(s, 3H), 1.10(d, $J=3.8\text{Hz}$, 6H).

Example 1042

3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]-2-pyrazinecarboxamide. ^1H NMR (300 MHz, CD_3OD) \square ppm 8.78(d, $J=2.5\text{Hz}$, 1H), 8.73(d, $J=2.5\text{Hz}$, 1H), 7.52(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 6.98(m, 1H), 4.74(m, 1H), 4.15(m, 1H), 3.46-1.68(m, 21H), 2.52(s, 3H).

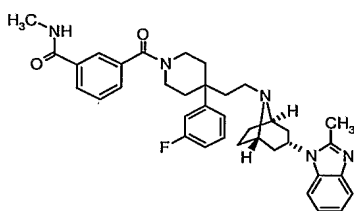
Example 1043

2-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]cyclobutanecarboxamide. ^1H NMR (300 MHz, CD_3OD) \square ppm 7.52(m, 1H), 7.40(m, 2H), 7.25-7.16(m, 4H), 6.97(m, 1H), 4.73(m, 1H), 4.15-1.68(m, 28H), 2.55(s, 3H).

Example 1045

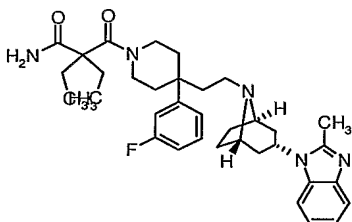
N-cyclopropyl-5-(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)-4,4-dimethyl-5-oxopentanamide. ^1H NMR (300 MHz, CD_3OD) δ ppm 7.52(m, 1H), 7.40(m, 2H), 7.25-7.12(m, 4H), 6.96(m, 1H), 4.75(m, 1H), 3.98(m, 1H), 3.36-1.68(m, 28H), 2.55(s, 3H).

Example 1050



3-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-N-methylbenzamide. ^1H NMR (300 MHz, CD_3OD) δ ppm 7.85(m, 1H), 7.84(m, 1H), 7.55(m, 3H), 7.40(m, 2H), 7.26-7.16(m, 4H), 7.00(m, 1H), 4.73(m, 1H), 4.13(m, 1H), 3.58(m, 1H), 3.46-1.68(m, 20H), 2.91(s, 3H), 2.51(s, 3H).

Example 1051

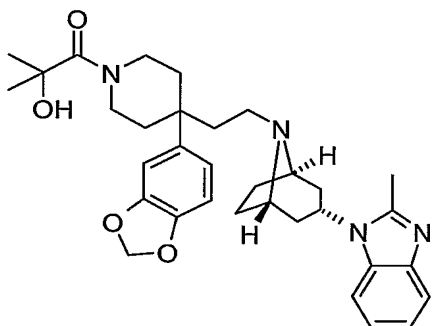


2-ethyl-2-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]butanamide. ^1H NMR (300 MHz, CD_3OD) δ 7.52(m, 1H), 7.41(m, 2H), 7.26-7.16(m, 4H), 6.98(m, 1H), 4.74(m, 1H), 3.97 (m, 1H), 3.67 (m, 1H), 3.34-3.21(m, 5H), 2.55(s, 3H), 2.41(m, 2H), 2.22(m, 2H), 2.03-1.69(m, 15H), 0.80(m, 6H).

Example 1168

Preparation of

1-(4-(1,3-benzodioxol-5-yl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2-methyl-1-oxopropan-2-ol

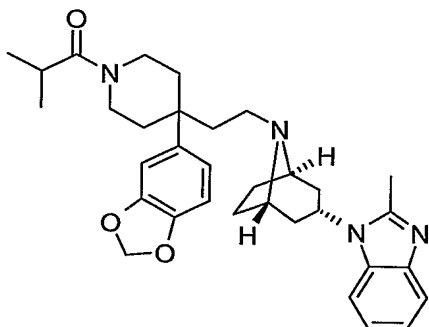


A mixture of 1-(8-{2-[4-(1,3-benzodioxol-5-yl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole dihydrochloride (0.20 g, 0.39 mmol), triethylamine (0.17 mL, 1.25 mmol) and 2-hydroxyisobutyric acid (41 mg, 0.39 mmol) in dimethylformamide (1.25 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (163 mg, 0.43 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate solution, with water, dried and purified by chromatography on silica gel eluting with a dichloromethane to methanol-dichloromethane 1:19 gradient to give 1-(4-(1,3-benzodioxol-5-yl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2-methyl-1-oxopropan-2-ol as a solid (0.10g, 44%). HRMS C₃₃H₄₂N₄O₄ *m/z* 559.3284 (M+H)_{Cal.} 559.3276 (M+H)_{Obs.}

Example 1169

Preparation of

1-((1*R*,5*S*)-8-{2-[4-(1,3-benzodioxol-5-yl)-1-isobutyrylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole

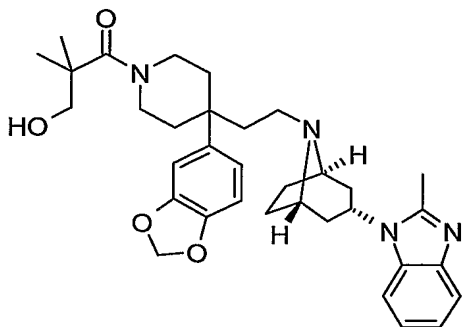


A mixture of 1-(8-{2-[4-(1,3-benzodioxol-5-yl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.20 g, 0.39 mmol), triethylamine (0.17 mL, 1.25 mmol) and isobutyric acid (34 mg, 0.39 mmol) in dimethylformamide (1.25 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (163 mg, 0.43 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting precipitate was collected, washed with saturated sodium bicarbonate solution, with water and dried to give 1-((1*R*,5*S*)-8-{2-[4-(1,3-benzodioxol-5-yl)-1-isobutyrylpiperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole as a solid (0.15g, 72%). HRMS $C_{33}H_{42}N_4O_3$ m/z 543.3335 ($M+H$)_{Cal.} 543.3322 ($M+H$)_{Obs.}

Example 1170

Preparation of

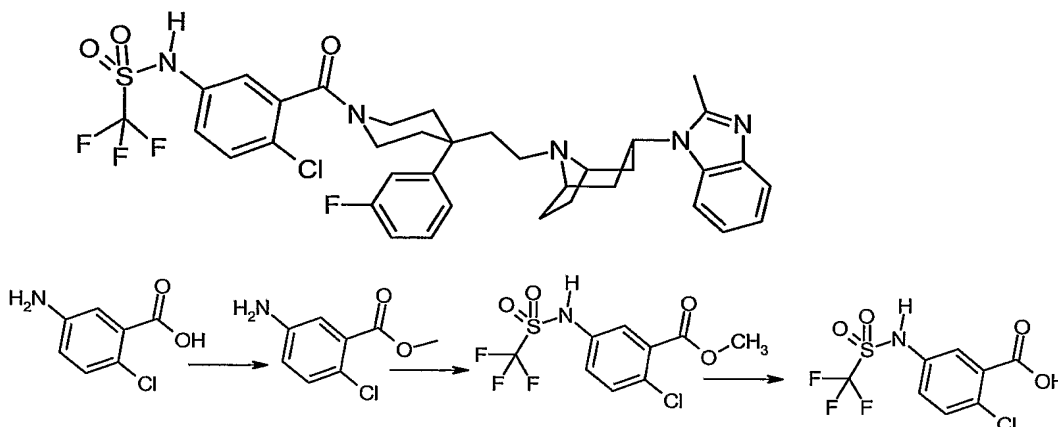
3-(4-(1,3-benzodioxol-5-yl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropan-1-ol



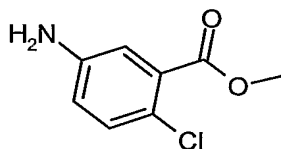
A mixture of 1-(8-{2-[4-(1,3-benzodioxol-5-yl)piperidin-4-yl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride (0.20 g, 0.39 mmol), triethylamine (0.17 mL, 1.25 mmol) and 2,2-dimethyl-3-hydroxypropionic acid (46 mg, 0.39 mmol) in dimethylformamide (1.25 mL) was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (163 mg, 0.43 mmol) and the resulting mixture was stirred for 1 h at rt. The mixture was diluted with water and the resulting gummy precipitate was dissolved in dichloromethane, washed with saturated sodium bicarbonate solution, with water, dried and purified by chromatography on silica gel eluting with a dichloromethane to methanol-dichloromethane 1:9 gradient to give 3-(4-(1,3-benzodioxol-5-yl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)-2,2-dimethyl-3-oxopropan-1-ol as a solid (0.13g, 59%). ¹H NMR (400 MHz, CDCl₃) δ 7.66 (m, 1H), 7.29 (m, 1H), 7.15 (m, 2H), 6.80 (m, 2H), 6.73 (m, 1H), 5.97 (s, 2H), 4.62 (m, 1H), 3.92 (m, 2H), 3.75 (m, 1H), 3.46 (s, 2H), 3.26 (m, 4H), 2.57 (s, 3H), 2.38 (m, 2H), 2.14 (m, 2H), 1.91 – 2.00 (m, 6H), 1.70 – 1.78 (m, 4H), 1.64 (m, 2H), 1.25 (s, 6H). HRMS C₃₄H₄₄N₄O₄ *m/z* 573.3441 (M+H)_{Cal.} 573.3428 (M+H)_{Obs.}

Example 1171

N-[4-chloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl]-1,1,1-trifluoromethanesulfonamide.



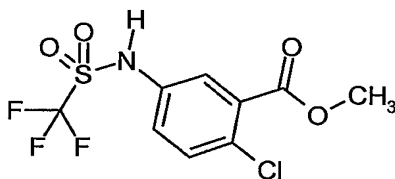
a) *Preparation of methyl 5-amino-2-chlorobenzoate.*



To a solution of 5-amino-2-chlorobenzoic acid (6.0 g, 35 mmol) in anhydrous methanol (100 ml) was added dropwise thionyl chloride (15 ml) with stirring under a nitrogen atmosphere. After stirring for 3 hours the volatiles were removed by spin evaporation in vacuo and the residue was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate and then water. The organic layer was concentrated by spin evaporation in vacuo with the addition of dichloromethane (3 times) to give methyl 5-amino-2-chlorobenzoate as a white solid (6.2 g, 95%). $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 7.20-7.14 (m, 1H), 7.13-7.02 (m, 1H), 6.73-6.67 (m, 1H), 3.89 (s, 3H). ES-LCMS m/z 186 ($\text{M}+\text{H}$).

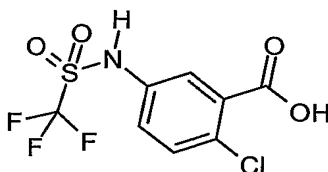
b) *Preparation of methyl 2-chloro-5-
{[(trifluoromethyl)sulfonyl]amino}benzoate.*

785



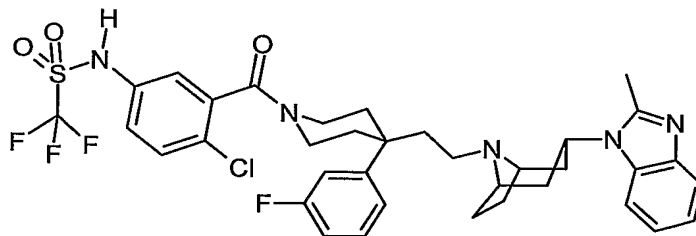
Triflic anhydride (1.53 g, 5.39 mmol) was added dropwise to a solution of methyl 5-amino-2-chlorobenzoate (2.0 g, 10.8 mmol) in dichloromethane (35 ml) at 0 °C while stirring under a nitrogen atmosphere. After warming to room temperature over 1 hour, the thick slurry was diluted with additional dichloromethane (200 ml) and washed with aqueous 1 N hydrochloric acid and then water. The dichloromethane layer was dried with MgSO_4 and the volatiles were removed by spin evaporation in vacuo to give methyl 2-chloro-5-[[[(trifluoromethyl)sulfonyl]amino]benzoate as a tan oil (1.7 g, 100%). ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.43 (s, 1H), 7.55-7.18 (m, 5H), 3.92-3.82 (m, 2H), 3.31-3.18 (m, 2H), 2.40-1.92 (m, 4H), and 1.38 (s, 9H). ES-LCMS m/z 317 (M+H).

c) *Preparation of 2-chloro-5-[[[(trifluoromethyl)sulfonyl]amino]benzoic acid.*



A solution of methyl 2-chloro-5-[[[(trifluoromethyl)sulfonyl]amino]benzoate (1.0 g, 3.15 mmol), sodium hydroxide (378 mg, 9.44 mmol), methanol (6 ml) and water (6 ml) was stirred for 1 hour. Removal of the volatiles by spin evaporation in vacuo gave a residue that was dissolved in 1 N aqueous hydrochloric acid. The aqueous solution was extracted with ethyl acetate (3 times) and the organic layers were combined, washed with water, and concentrated by spin evaporation in vacuo to give 2-chloro-5-[[[(trifluoromethyl)sulfonyl]amino]benzoic acid as a crystalline solid (0.78 g, 82%). ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.63-7.60 (m, 1H), 7.59-7.54 (m, 1H), 7.40-7.35 (m, 1H). ES-LCMS m/z 304 (M+H).

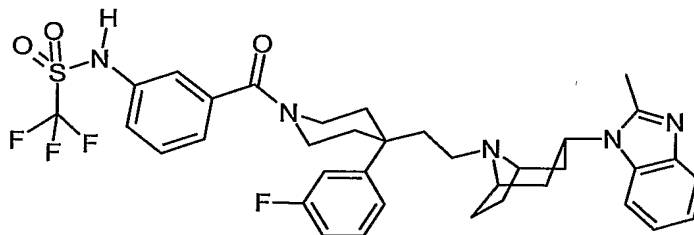
d) Preparation of *N*-{4-chloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide.



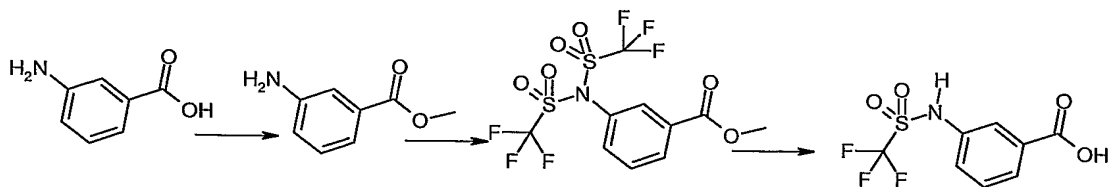
N-{4-Chloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}piperidin-1-yl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide (43m g, 23 %) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol), 2-chloro-5-[[[(trifluoromethyl)sulfonyl]amino]benzoic acid (82 mg, 270 mmol), HATU (140 mg, 389 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ¹H-NMR (400 MHz, DMSO-*d*₆): 8.6 (bs, 1H), 7.56-7.38 (m, 3H), 7.32-7.06 (m, 6H), 6.96-6.77 (m, 2H), 4.90-4.76 (bs, 1H), 4.04-3.82 (m, 3H), 3.40-3.15 (m, 5H+H₂O), 3.07-2.94 (m, 1H), 2.64-2.36 (m, 2H+DMSO), 2.23-1.68 (m, 14H). ES-LCMS *m/z* 732 (M+H).

Example 1172

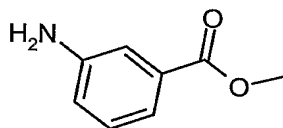
1,1,1-Trifluoro-*N*-{3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide



787

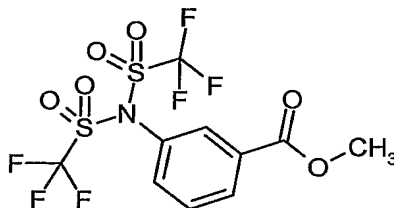


a) *Preparation of methyl 3-amino-benzoate.*



To a solution of 3-amino-benzoic acid (10.0 g, 72 mmol) in anhydrous methanol (100 ml) was added dropwise acetyl chloride (15 ml) with stirring under a nitrogen atmosphere. After stirring for 3 hours the volatiles were removed by spin evaporation in vacuo and the residue was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate and then water. The organic layer was concentrated by spin evaporation in vacuo with the addition of dichloromethane (3 times) give methyl 5-amino-2-chlorobenzoate as a white solid. (9.8 g, 89%). $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$, δ 7.92-7.78 (m, 2H), 7.50-7.44 (m, 1H), 7.4-7.36 (m, 1H), 3.94 (s, 3H) ES-LCMS m/z 152 (M+H).

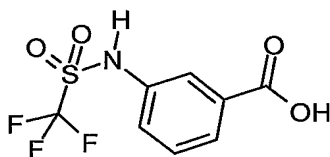
b) *Preparation of methyl 3-{bis[(trifluoromethyl)sulfonyl]amino}benzoate.*



Triflic anhydride (3.73 g, 13.2 mmol) was added dropwise to a solution of methyl 3-amino-benzoate (2.0 g, 13.2 mmol) and DIEA (2.3 ml) in dichloromethane (50 ml) at 0 °C while stirring under a nitrogen atmosphere. After warming to room temperature over 1 hour, the thick slurry was diluted with additional dichloromethane (200 ml) and washed with aqueous 1 N hydrochloric acid and the water. The dichloromethane layer was dried with

MgSO₄ and the volatiles were removed by spin evaporation in vacuo to give methyl 3-bis[(trifluoromethyl)sulfonyl]amino}benzoate as a tan oil (5.4 g, 100%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.73-7.65 (m, 2H), 7.55-7.50 (m, 1H), 7.44-7.36 (m, 1H), 3.95 (s, 3H). ES-LCMS *m/z* 416 (M+H).

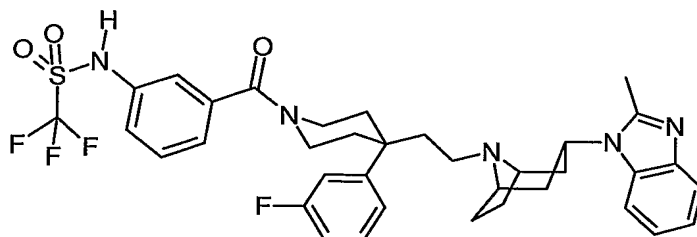
c) Preparation of 3-[[[(trifluoromethyl)sulfonyl]amino}benzoic acid.



A solution of methyl 3-bis[(trifluoromethyl)sulfonyl]amino}benzoate (5.4 g, 13.0 mmol), sodium hydroxide (3.12 g, 78.0 mmol), methanol (125 ml) and water (125 ml) was stirred for 2 hours. The solution from concentration to 75 ml by spin evaporation in vacuo and dilution with 100 ml water was extracted with ethyl acetate. The aqueous layer was acidified with 12 N hydrochloric acid and again extracted with ethyl acetate. The organic layer was washed with water and concentrated by spin evaporation in vacuo, with the addition of dichloromethane (3 times) to give a residue that was dissolved in 1 N aqueous hydrochloric acid. The aqueous solution was extracted with ethyl acetate (3 times) and the organic layers were combined, washed with water, and concentrated by spin evaporation in vacuo to 3-[[[(trifluoromethyl)sulfonyl]amino}benzoic acid as a solid (2.3 g, 66%). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.83-7.78 (m, 2H), 7.55-7.50 (m, 1H), 7.50-7.46 (m, 1H). ES-LCMS *m/z* 269 (M+H).

d) Preparation of 1,1,1-trifluoro-N-{3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide.

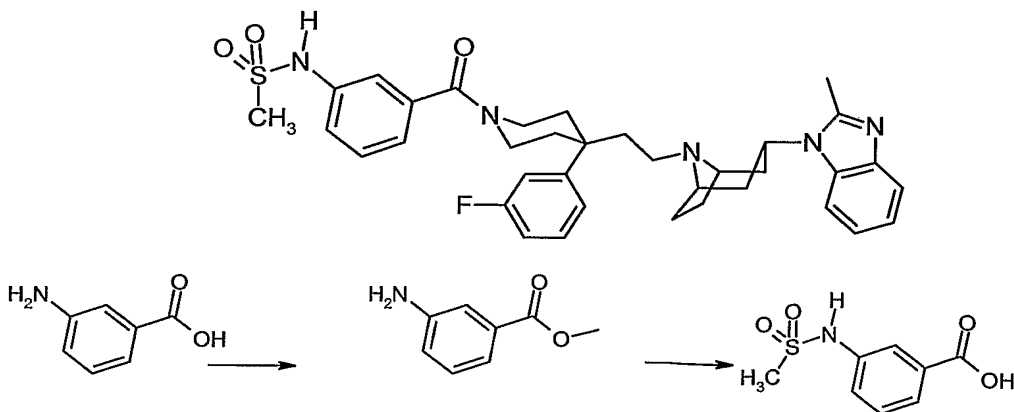
789



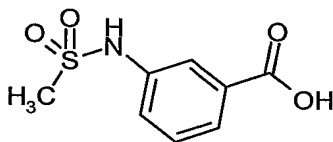
1,1,1-Trifluoro-*N*-{3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide (72 mg, 100%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol), 3-[(trifluoromethyl)sulfonyl]amino}benzoic acid (73 mg, 270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 8.83-8.68 (bs, 1H), 7.58-7.49 (m, 1H), 7.59-7.49 (m, 2H), 7.49-7.38 (m, 2H), 7.21-7.05 (m, 4H), 7.02-6.91 (m, 2H), 6.79-6.67 (m, 1H), 5.03-4.76 (m, 1H), 4.13-3.96 (m, 3H), 3.57-3.01 (m, 6H), 2.54-2.39 (M, 5H), 2.24-1.97 (m, 8H), 1.97-1.68 (m, 3H), 1.31-1.14 (m, 2H). ES-LCMS m/z 698 ($\text{M}+\text{H}$).

Example 1173

N-{3-[(4-(3-Fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide

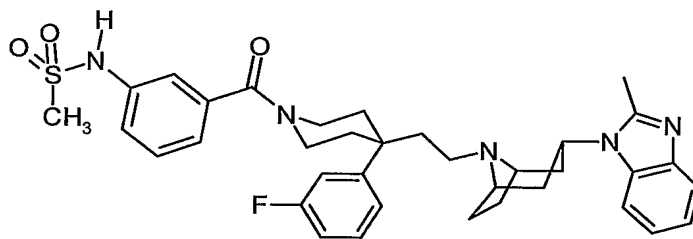


a) Preparation of 3-[(methylsulfonyl)amino]benzoic acid.



To a solution of methyl 3-amino-benzoate (2.0 g, 13.2 mmol) and pyridine (2.30 g, 29.1 mmol) in dichloromethane (50 ml) at -10°C under a nitrogen atmosphere was slowly added methanesulfonyl chloride (2.25 ml, 29.1 mmol) by syringe. After 2 hours, water was added and the volatiles were removed by spin evaporation in vacuo. A solution of the residue and sodium hydroxide (3.175 g, 79.4 mmol) in methanol (50 ml) and water (50 ml) was stirred for 18 hours. The residue after removal of the volatiles by spin evaporation in vacuo was dissolved in 1 N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and the volatiles were removed by spin evaporation in vacuo to give 3-[(methylsulfonyl)amino]benzoic acid as an oil. (1.32 g, 46 %). $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 7.83-7.78 (m, 2H), 7.55-7.50 (m, 1H), 7.50-7.46 (m, 1H), 3.80 (s, 3H). ES-LCMS m/z 216 (M+H).

b) Preparation of N-{3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide.

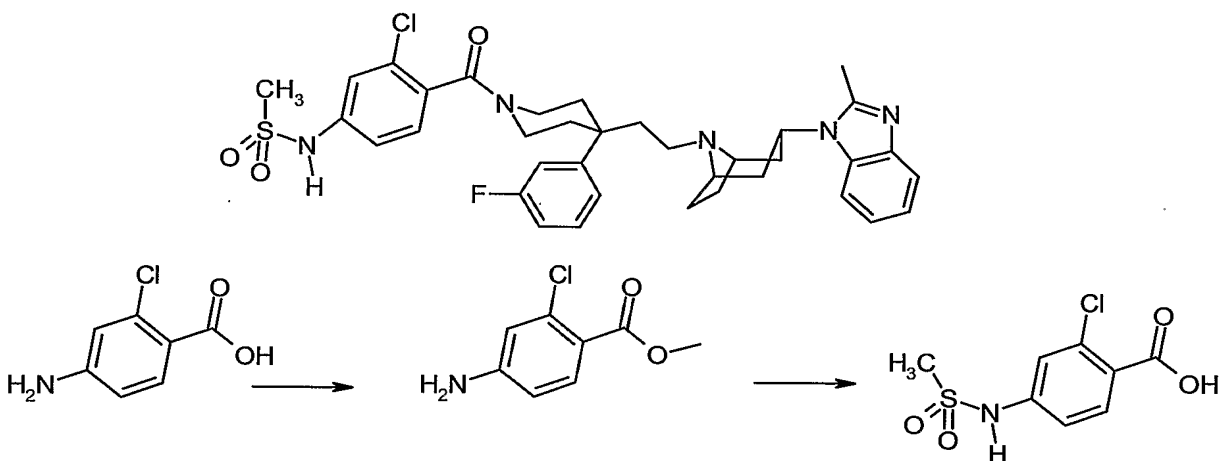


N-{3-[(4-(3-Fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide (72 mg, 100%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidiny]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 μmol 3-

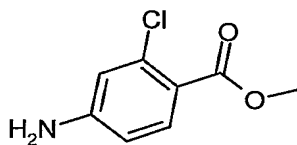
[(methylsulfonyl)amino]benzoic acid (73 mg, 270 μ mol), HATU (140 mg, 369 μ mol), and DIEA (95 mg, 738 μ mol) following the procedure outlined in example 5. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 9.90 (bs 1H), 7.49-7.49 (m, 1H), 7.44-7.31 (m, 3H), 7.27-7.20 (m, 3H), 7.19-7.15 (m, 1H), 7.14-7.00 (m, 4H), 4.55-4.39 (m, 1H), 3.91-3.79 (m, 1H), 3.53-3.40 (m, 1H), 3.40-3.09 (m, 2H), 3.03-2.96 (m, 3H), 2.51-2.45 (m, 5H), 2.44-2.40 (m, 3H), 2.40-2.30 (m, 2H), 2.17-1.96 (m, 2H), 1.91-1.70 (m, 4H), 1.64-1.52 (m, 2H), 1.25-1.10 (m, 1H). ES-LCMS m/z 644 ($M+H$).

Example 1174

N-{3-Chloro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.



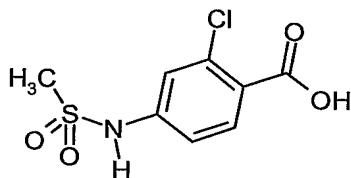
a) *Preparation of methyl 4-amino-2-chlorobenzoate.*



Methyl 4-amino-2-chlorobenzoate (5.1 g, 94 %) was obtained as solid from 4-amino-2-chlorobenzoic acid (5.0 g, 29.1 μ mol) following the procedure outlined for **methyl 5-amino-2-chlorobenzoate**. $^1\text{H-NMR}$ (400 MHz, DMSO-

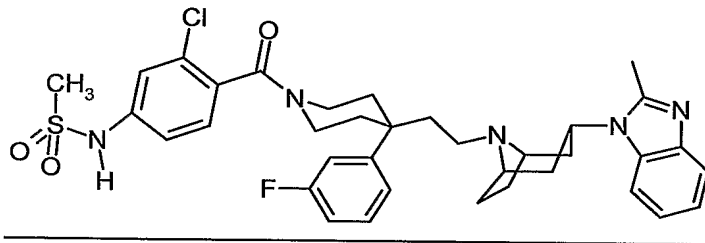
d_6): δ 7.64-7.57 (m, 1H), 6.65-6.57 (m, 1H), 6.51-6.39 (m, 1H), 6.16 (bs, 2H), 3.71 (s, 3H). ES-LCMS m/z 186 (M+H).

b) Preparation of 2-chloro-4-[(methylsulfonyl)amino]benzoic acid.



2-Chloro-4-[(methylsulfonyl)amino]benzoic acid (5.1 g, 94 %) was obtained as an oil from methyl 4-amino-2-chlorobenzoate (5.0 g, 29.1 mmol) following the procedure outlined for **3-[(methylsulfonyl)amino]benzoic acid**. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 13.11 (bs, 1H), 10.29 (bs, 1H), 7.83-7.80 (m, 1H), 7.24-7.22 (m, 1H), 7.21-7.18 (m, 1H), 3.11 (s, 3H). ES-LCMS m/z 250 (M+H).

c) Preparation of N-{3-chloro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide.

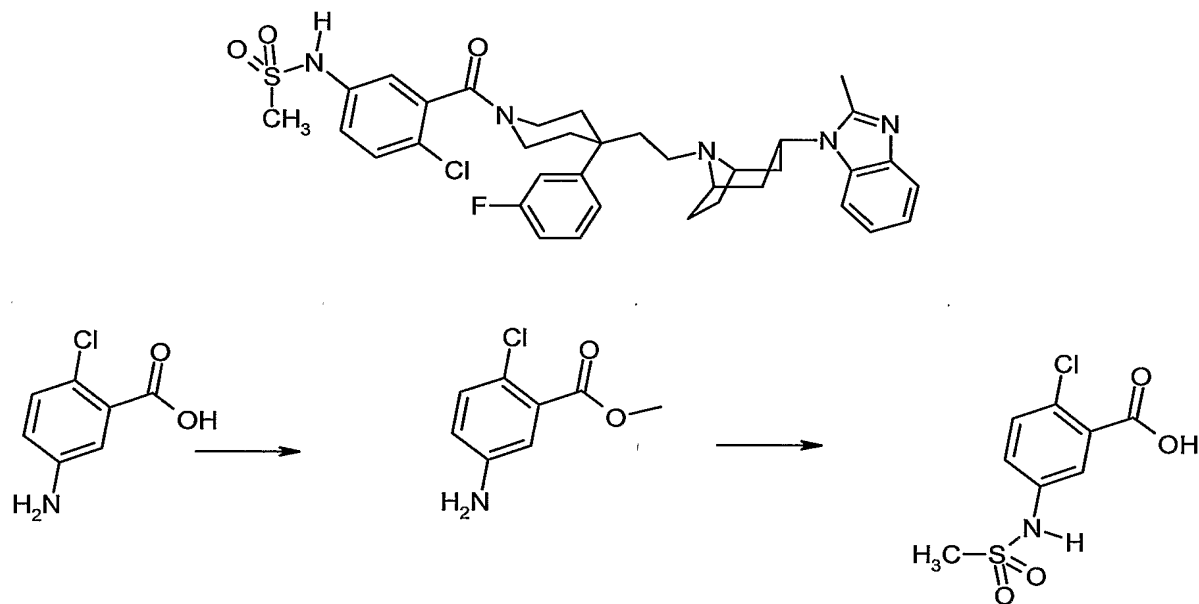


N-{3-Chloro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide (29 mg, 17.4%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidiny]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (150 mg, 246 mmol), 2-chloro-4-[(methylsulfonyl)amino]benzoic acid (68 mg, 0.270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure

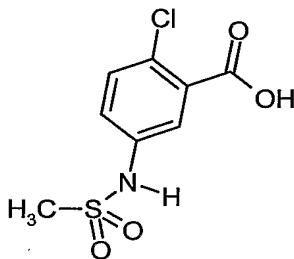
outlined in example 5. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 7.55-7.44 (m, 1H), 7.44-7.27 (m, 3H), 7.27-6.98 (m, 8H), 4.56-4.42 (m, 1H), 3.97-3.82 (m, 1H), 3.39-3.17 (m, 3H), 3.10-2.93 (m, 5H), 2.44-2.40 (m, 3H), 2.39-2.29 (m, 2H), 2.19-2.02 (m, 3H), 1.93-1.69 (m, 6H), 1.62-1.54 (m, 2H), 1.24-1.07 (m, 2H), 0.98-0.91 (m, 1H). ES-LCMS m/z 678 (M+H).

Example 1175

N-{4-chloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide



a) *Preparation of 2-chloro-5-[(methylsulfonyl)amino]benzoic acid.*

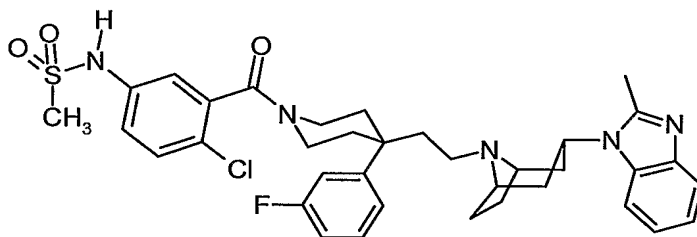


2-Chloro-5-[(methylsulfonyl)amino]benzoic acid (1.83 g, 68 %) was obtained as an oil from methyl 5-amino-2-chlorobenzoate (2.0 g, 10.8 mmol)

following the procedure outlined for **2-chloro-4-**

[(methylsulfonyl)amino]benzoic acid. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 13.46 (bs, 1H), 10.05 (s, 1H), 7.62-7.55 (m, 1H), 7.50-7.45 (m, 1H), 7.37-7.30 (m, 1H), 3.02 (s, 3H). ES-LCMS m/z 249 (M+H).

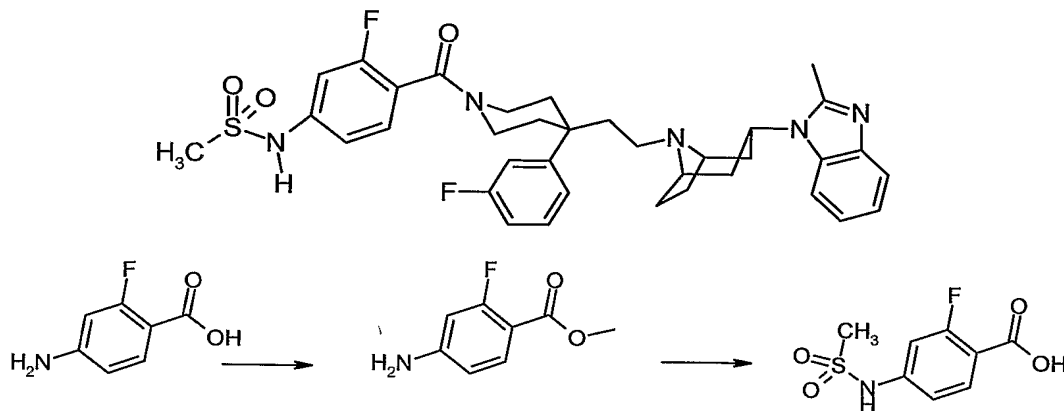
b) Preparation of *N*-{4-chloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide.



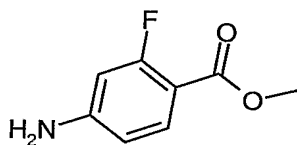
N-{4-Chloro-3-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide (103 mg, 61.6 %) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidiny]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (150 mg, 246 μmol) 2-chloro-5-[(methylsulfonyl)amino]benzoic acid (68 mg, 0.270 μmol), HATU (140 mg, 369 μmol), and DIEA (95 mg, 738 μmol) following the procedure outlined in example 5. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 10.00 (bs, 1H), 7.57-7.47 (m, 2H), 7.45-7.34 (m, 2H), 7.28-7.21 (m, 3H), 7.18-7.02 (m, 4H), 4.57-4.43 (m, 1H), 3.98-3.83 (m, 1H), 3.45-3.21 (m, 8H), 3.11-2.99 (m, 4H), 2.46-2.41 (m, 3H), 2.41-2.30 (m, 2H), 2.21-2.02 (m, 2H), 1.99-1.72 (m, 6H), 1.65-1.56 (m, 2H). ES-LCMS m/z 678 (M+H).

Example 1176

N-{3-Fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.

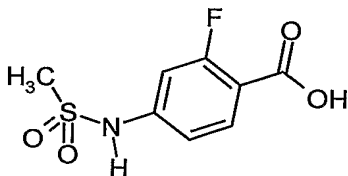


a) Preparation of methyl 4-amino-2-fluorobenzoate.



Methyl 4-amino-2-fluorobenzoate (1.98 g, 98 %) was obtained as solid from 4-amino-2-fluorobenzoic acid (2.0 g, 12.90 mmol) following the procedure outlined for **methyl 5-amino-2-chlorobenzoate**. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.61-7.58 (m, 1H), 6.42-6.37 (m, 1H), 6.32-6.25 (m, 3H), 3.72 (s, 3H). ES-LCMS *m/z* 170 (M+H).

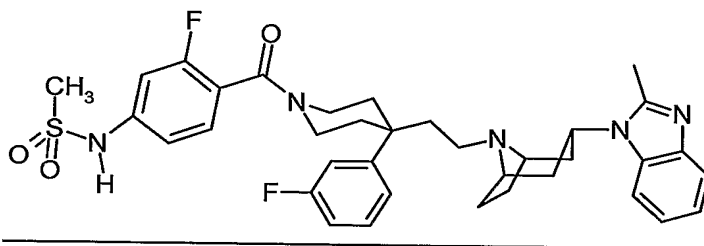
b) Preparation of 2-fluoro-4-[(methylsulfonyl)amino]benzoic acid.



2-Fluoro-4-[(methylsulfonyl)amino]benzoic acid (5.1 g, 94 %) was obtained as an oil from methyl 4-amino-2-fluorobenzoate (5.0 g, 29.1 mmol) following the procedure outlined in example 3-**[(methylsulfonyl)amino]benzoic acid**. ¹H-NMR (400 MHz, DMSO-*d*₆): δ

7.69-7.59 (m, 1H), 6.45-6.40 (m, 1H), 6.40-6.32 (m, 3H), 3.72 (s, 3H). ES-LCMS m/z 234 (M+H).

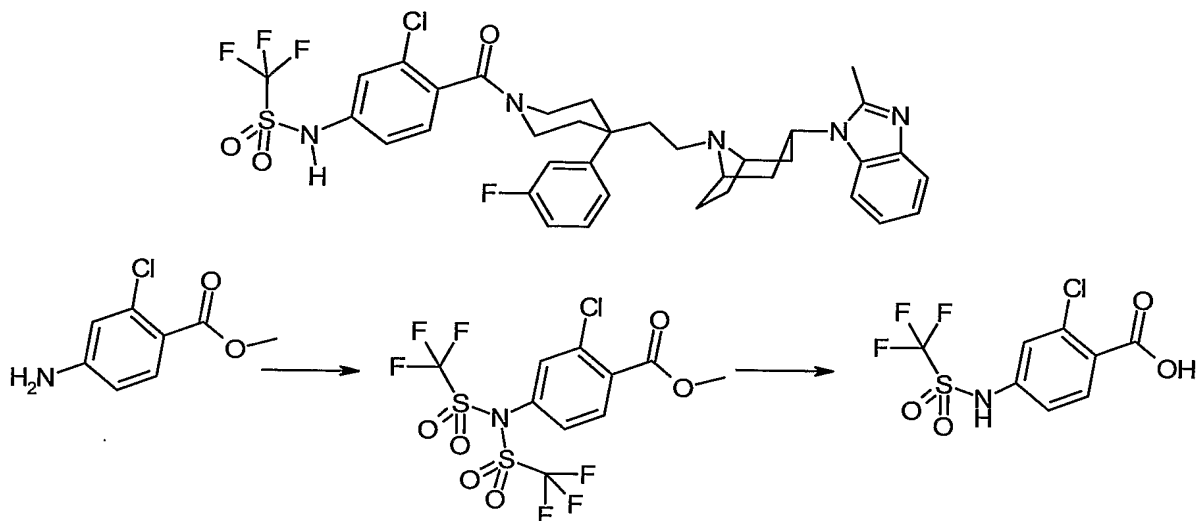
c) Preparation of *N*-{3-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.



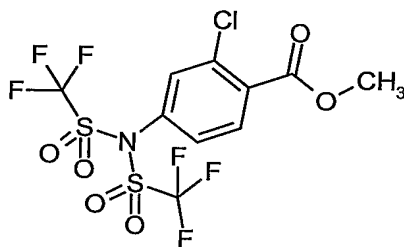
N-{3-Fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide (26 mg, 15%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (150 mg, 246 μ mol), 2-chloro-4-[(methylsulfonyl)amino]benzoic acid (U20375/163/1) (68 mg, 0.270 mmol), HATU (140 mg, 369 μ mol), and DIEA (95 mg, 738 μ mol) following the procedure outlined in example 5. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 7.49-7.45 (m, 1H), 7.43-7.28 (m, 3H), 7.25-7.01 (m, 8H), 4.54-4.42 (m, 1H), 3.95-3.83 (m, 1H), 3.38-3.196 (m, 5H+H₂O), 3.08-2.97 (m, 4H), 2.51-2.40 (m, 2H), 2.39-2.29 (m, 2H), 2.18-2.01 (m, 3H), 1.91-1.70 (m, 6H), 1.62-1.55 (m, 2H), 1.23-1.10 (m, 2H), 0.98-0.92 (m, 1H). ES-LCMS m/z 662 (M+H).

Example 1177

N-{3-Chloro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide



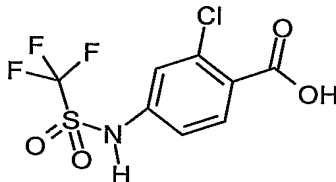
b) *Preparation of methyl 4-bis[(trifluoromethyl)sulfonyl]amino}-2-chlorobenzoate.*



Triflic anhydride (3.73 g, 13.2 mmol) was added dropwise to a solution of methyl 4-amino-2-chlorobenzoate (2.45 g, 13.2 mmol) and ethyl[bis(1-methylethyl)]amine (2.3 ml) in dichloromethane (50 ml) at 0 °C while stirring under a nitrogen atmosphere. After warming to room temperature over 1 hour, the thick slurry was diluted with additional dichloromethane (200 ml) and washed with aqueous 1 N hydrochloric acid and the water. The dichloromethane layer was dried with MgSO₄ and the volatiles were removed by spin evaporation in vacuo to give methyl 4-

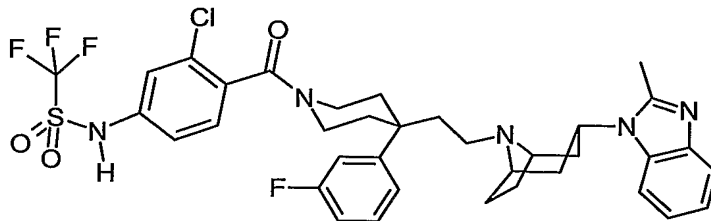
{bis[(trifluoromethyl)sulfonyl]amino}-2-chlorobenzoate as a tan oil (5.9 g, 100 %). ES-LCMS m/z 450 (M+H).

c) Preparation of 2-chloro-4-[[[(trifluoromethyl)sulfonyl]amino]benzoic acid.



A solution of methyl 4-{bis[(trifluoromethyl)sulfonyl]amino}-2-chlorobenzoate (5.9 g, 13.1 mmol), sodium hydroxide (3.12 g, 78.0 mmol), methanol (125 ml) and water (125 ml) was stirred for 2 hours. The solution from concentration to 75 ml by spin evaporation in vacuo and dilution with 100 ml water was extracted with ethyl acetate. The aqueous layer was acidified with 12 N hydrochloric acid and again extracted with ethyl acetate. The organic layer was washed with water and concentrated by spin evaporation in vacuo, with the addition of dichloromethane (3 times) to give a residue that was dissolved in 1 N aqueous hydrochloric acid. The aqueous solution was extracted with ethyl acetate (3 times) and the organic layers were combined, washed with water, and concentrated by spin evaporation in vacuo 2-chloro-4-[[[(trifluoromethyl)sulfonyl]amino]benzoic acid as a solid (3.6 g, 61%). ES-LCMS m/z 304 (M+H).

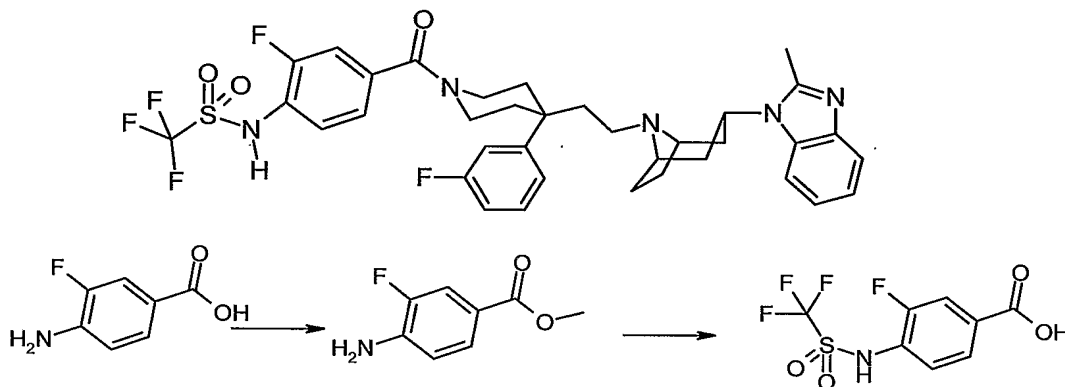
d) Preparation of N-{3-chloro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide.



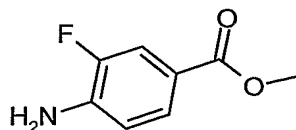
N-{3-chloro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}-1,1,1-trifluoromethanesulfonamide (35 mg, 19%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (150 mg, 246 mmol), 2-chloro-4-[[[(trifluoromethyl)sulfonyl]amino]benzoic (82 mg, 270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ES-LCMS *m/z* 732 (M+H).

Example 1178

1,1,1-Trifluoro-*N*-{2-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.

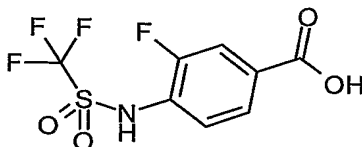


a) Preparation of Methyl 4-amino-3-fluorobenzoate.



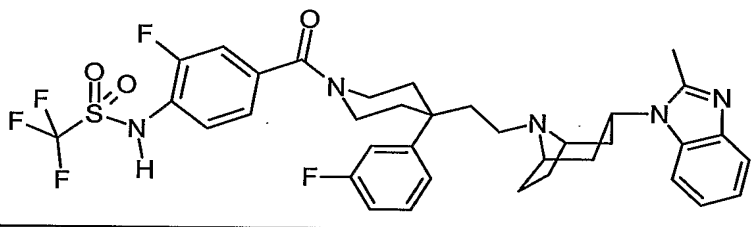
Methyl 4-amino-3-fluorobenzoate (1.01 g, 92 %) was obtained as solid from 4-amino-3-fluorobenzoic acid (1.0 g, 6.4 mmol) following the procedure outlined in example 1171. ES-LCMS *m/z* 170 (M+H).

b) Preparation of 3-fluoro-4-[[trifluoromethyl)sulfonyl]amino]benzoic acid.



3-Fluoro-4-[[trifluoromethyl)sulfonyl]amino]benzoic acid (0.892 g, 97 %) was obtained as an oil from methyl 4-amino-3-fluorobenzoate (1.80 g, 6.39 mmol)) following the procedure outlined in example 1174. ES-LCMS m/z 288 (M+H).

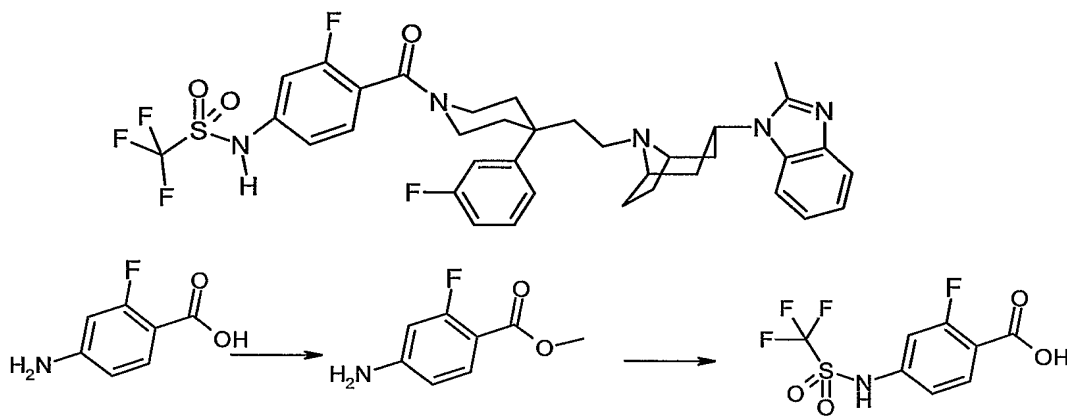
c) Preparation of 1,1,1-trifluoro-N-{2-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.



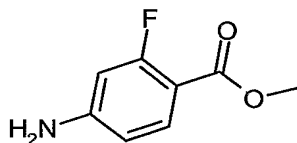
1,1,1-Trifluoro-N-{2-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide (85 mg, 48%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (150 mg, 246 mmol), 3-fluoro-4-[[trifluoromethyl)sulfonyl]amino]benzoic acid (78 mg, 270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ES-LCMS m/z 716 (M+H).

Example 1179

1,1,1-Trifluoro-N-{3-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.

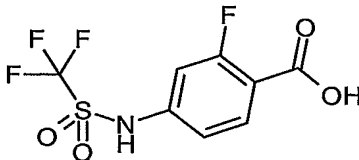


a) Preparation of methyl 4-amino-2-fluorobenzoate.



Methyl 4-amino-2-fluorobenzoate (1.85 g, 84 %) was obtained as solid from 4-amino-2-fluorobenzoic acid (2.0 g, 12.90 mmol) following the procedure outlined in example 1171. ES-LCMS m/z 170 (M+H).

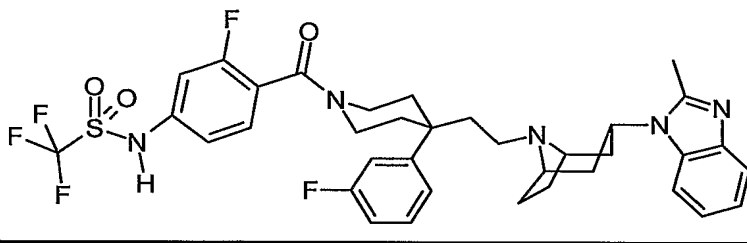
b) Preparation of 2-fluoro-4-[(trifluoromethyl)sulfonyl]amino}benzoic acid.



2-Fluoro-4-[(trifluoromethyl)sulfonyl]amino}benzoic acid (1.32 g, 74 %) was obtained as an oil from methyl 4-amino-2-fluorobenzoate (1.05 g, 6.2

mmol)) following the procedure outlined in example 1174. ES-LCMS m/z 288 (M+H).

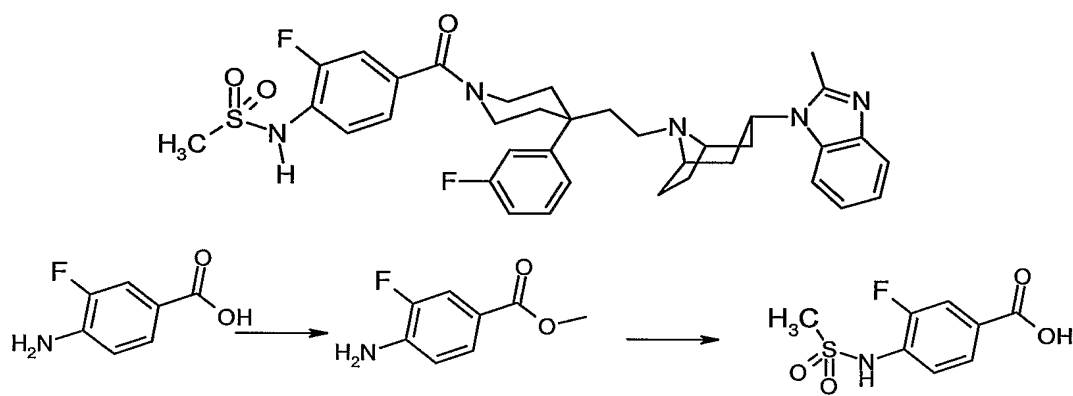
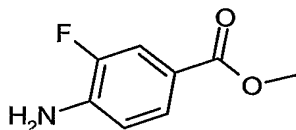
c) Preparation of 1,1,1-trifluoro-N-{3-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide.



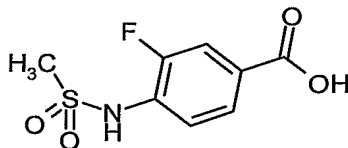
1,1,1-Trifluoro-N-{3-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide (85 mg, 48%) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidiny]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (150 mg, 246 mmol), 2-fluoro-4-{[(trifluoromethyl)sulfonyl]amino}benzoic acid (78 mg, 270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ES-LCMS m/z 716 (M+H).

Example 1180

N-{2-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]phenyl}methanesulfonamide.

**a) Preparation of methyl 4-amino-3-fluorobenzoate**

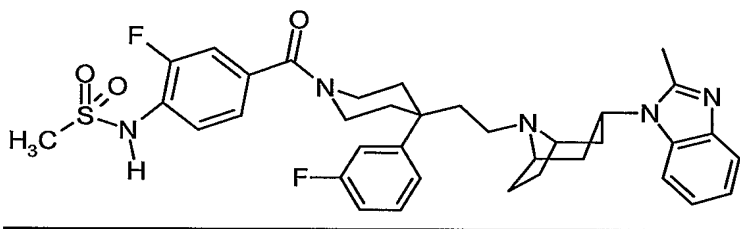
Methyl 4-amino-3-fluorobenzoate (0.98 g, 90.0 %) was obtained as solid from 4-amino-3-fluorobenzoic acid (1.0 g, 6.45 mmol)) following the procedure outlined in example 1171. ES-LCMS *m/z* 170 (M+H).

b) Preparation of 3-fluoro-4-[(methylsulfonyl)amino]benzoic acid.

3-Fluoro-4-[(methylsulfonyl)amino]benzoic acid (490 mg, 66 %) was obtained as an oil from methyl 4-amino-3-fluorobenzoate (0.54 g, 3.19 mmol)

) following the procedure outlined in example 1174. ES-LCMS m/z 234 (M+H).

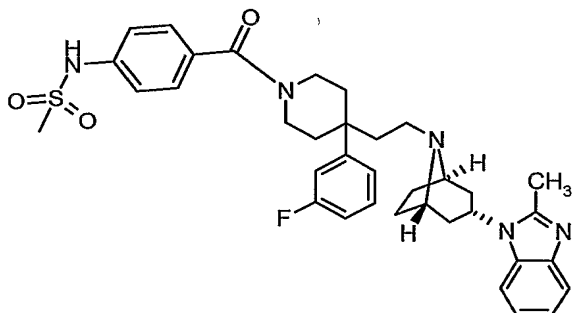
c) Preparation of N-{2-fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide.



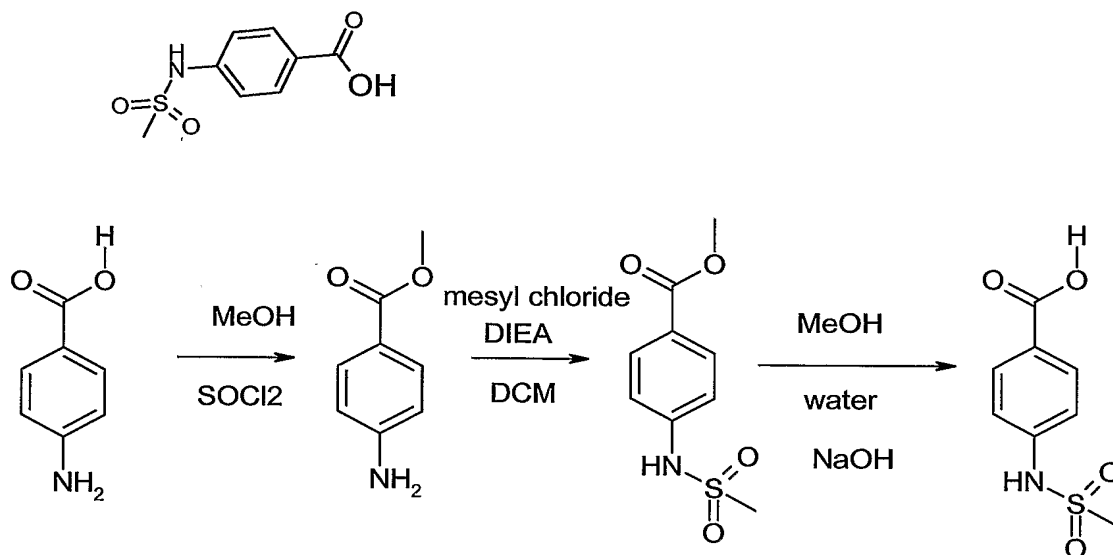
N-{2-Fluoro-4-[(4-(3-fluorophenyl)-4-{2-[3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide (92 mg, 52 %) was obtained as a solid from 1-(8-{2-[4-(3-fluorophenyl)-4-piperidiny]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole (150 mg, 246 mmol), 3-fluoro-4-[(methylsulfonyl)amino]benzoic acid (U20375/147/1) (78 mg, 270 mmol), HATU (140 mg, 369 mmol), and DIEA (95 mg, 738 mmol) following the procedure outlined in example 5. ES-LCMS m/z 662 (M+H).

Example 1181

N-{4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide



The synthesis of 4-[(methylsulfonyl)amino]benzoic acid



2.1 g (15.6 mmol) of 4-aminobenzoic acid was dissolved in anhydrous MeOH, added 14.47g (123.3 mmol) of thionyl chloride dropwise under N₂ while stirring at rt. After stirring for four hours, solvents were removed and redissolved in 100 mL EtOAc and 40 mL of saturated NaHCO₃ aq, stirred 30 min, separated and washed with 3 x 20 mL water. Organics were dried yielding 2.17g (yield 92.1%) of methyl 4-aminobenzoate. ¹H NMR (300 MHz, CDCl₃): 7.88 (2H, d, *J*=8.6 Hz), 6.66 (2H, d, *J*=8.6 Hz), 4.19 (2H, broad s), 3.88 (3H, s). ¹³C NMR (300 MHz, CDCl₃): 167.8 (C=O), 151.4 (Cq), 131.9 (2x CH), 120.0 (Cq), 113.8 (2x CH), 50.9 (CH₃).

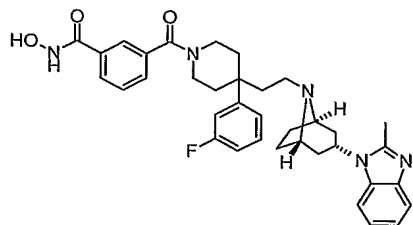
1.13g (7.48 mmol) of methyl 4-aminobenzoate was dissolved in 20 mL of anhydrous DCM and 1.97g (17.19 mmol) of mesyl chloride was added at 4 deg C, followed by the 2.22 g (17.19 mmol) of the diethylisopropylamine. Reaction was carried out overnight at room temperature resulting methyl 4-[(methylsulfonyl)amino]benzoate, which was used in the next step without additional purification.

3.6 g (90 mmol) of NaOH was added to the solution of methyl 4-[(methylsulfonyl)amino]benzoate in 40 mL methanol and 20 mL water and stirred overnight at room temperature. Solvents were then removed and the product purified by ethyl acetate extraction from 1N aqueous hydrochloric acid, providing 1.2g (yield 74.6%) of the 4-[(methylsulfonyl)amino]benzoic acid. ¹H NMR in d-chloroform: 8.03 (2H, d, J=8.7 Hz), 7.34 (2H, d, J=8.7 Hz), 3.09 (3H, s). ¹³C NMR in d-chloroform: 131.2, 117.9, 38.6.

The synthesis of N-{4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide

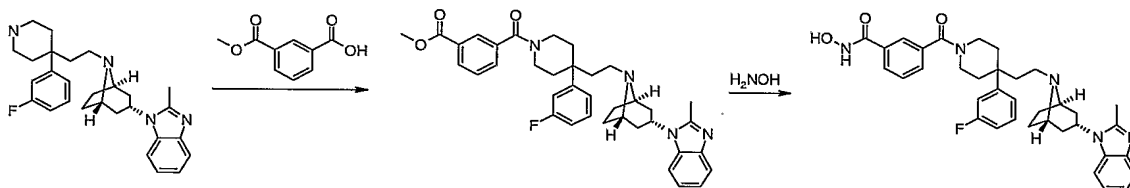
270 mg (0.61 mmol) of 1-((1R,5S)-8-{2-[4-(3-fluorophenyl)-4-piperidiny]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1H-benzimidazole dihydrochloride salt trihydrate was dissolved in the dichloromethane, and added 195 mg (0.91 mmol) of the 4-[(methylsulfonyl)amino]benzoic acid, 440 mg (0.91 mmol) of HATU and 391 mg (3.03 mmol) of the diethylisopropylamine an the reaction carried out as described in example 5, resulting in title N-{4-[(4-(3-fluorophenyl)-4-{2-[(1R,5S)-3-(2-methyl-1H-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidiny]carbonyl]phenyl}methanesulfonamide, yield 32% after HPLC purification.

¹H NMR (d4-methanol, 400 MHz): 7.53 (1H, m), 7.40 (4H, m), 7.31 (2H, d, J=7.7 Hz), 7.22 (4H), 6.99 (1H, m), 4.74 (1H, m), 4.09 (1H, broad s), 3.68 (1H, broad s), 3.39 (4H, m), 3.03 (4H, m), 2.52 (s, 3H), 2.45 (2H, m), 2.32 (1H, broad s), 2.23 (1H, broad s), 1.95 (10H, m), 1.71 (1H, m)

Example 1074

3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-*N*-hydroxybenzamide

Example 1074 was prepared according to scheme below.



1-((1*R*,5*S*)-8-{2-[4-(3-fluorophenyl)-4-piperidinyl]ethyl}-8-azabicyclo[3.2.1]oct-3-yl)-2-methyl-1*H*-benzimidazole (500mg, 0.962mmol) was combined with 3-[(methoxy)carbonyl]benzoic acid (173mg, 0.962mmol) and DIPEA (373mg, 2.88mmol) in 8mL DMF and treated with HATU (366mg, 0.962mmol) at ambient temperature for 16h. The reaction mixture was treated with satd. NaHCO₃ which yielded a solid precipitate that was filtered off, washed with water and dried to give methyl 3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzoate (395mg, 0.649mmol, 67%) as a white solid. ES-LCMS *m/z* 609.1 (M+H).

Hydroxylamine.HCl (26mg, 0.360mmol) dissolved in 5mL EtOH was cooled in an ice bath and treated with 0.5M NaOCH₃ (1.92mL, 0.96mmol) for 15min with stirring. Methyl 3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]benzoate (183mg, 0.300mmol) was added to the reaction

mixture and allowed to stir 16h at ambient temperature. The reaction mixture was concentrated to dryness and purified by RP-HPLC on a C-18 column eluted with 0→50%CH₃CN in H₂O with 0.1% formic acid buffer. The appropriate fractions were combined and concentrated to give 3-[(4-(3-fluorophenyl)-4-{2-[(1*R*,5*S*)-3-(2-methyl-1*H*-benzimidazol-1-yl)-8-azabicyclo[3.2.1]oct-8-yl]ethyl}-1-piperidinyl)carbonyl]-*N*-hydroxybenzamide (20mg, 0.032mmol, 9%) as a clear glass. ES-LCMS *m/z* 610.14 (M+H), 608.21 (M-1).

CC-Chemokine Receptor-5 Binding by Scintillation Proximity Assay

The compounds of this invention were evaluated as antagonists of CCR5 by high-throughput screening using scintillation proximity assay (SPA) binding that measures inhibition of binding of ¹²⁵I-MIP1□ to the human CCR5 chemokine receptor.

Human CCR5 receptors were expressed in Chinese Hamster Ovary (CHO) cells. Cells were grown in suspension and 50 to 80 ml CCR5 cell pellets were prepared.

Membranes were prepared according to the following procedure: 1) weighed pellet; 2) prepared an ice-cold 50 mM HEPES buffer, containing 0.0025 mg/ml Pefabloc, 0.0001 mg/ml Pepstatin A, 0.0001 mg/ml Leupeptin, 0.0001 mg/ml Aprotinin (protease inhibitor cocktail), pH 7.4; 3) homogenized pellet in 5 volumes of HEPES buffer; 4) homogenized again with a glass homogenizer for 10 to 20 strokes; 5) centrifuged homogenate at 18,000 rpm in a F28/36 rotor using a Sorvall RC26 PLUS refrigerated Centrifuge for 30 minutes; 6) discarded supernatant and resuspended pellet in 3 volumes of HEPES buffer; 7) homogenized and centrifuged again using steps 4-6 for two more times; 8) re-weighed pellet and homogenize in three times weight-to-volume of HEPES buffer; 9) placed aliquot 0.5 to 1.5 ml of the membrane preparation into small vials and stored at -80°C; 10) determined the protein concentration of the membrane preparation using the Bio-Rad or BCA

method; and 11) characterized the membrane homogenate for the assay conditions including protein concentration, optimal protein-to-bead ratio in SPA, and saturation curve to determine K_d and B_{max} (number of binding sites) in SPA.

The saturation curve binding experiment was performed by adding varying amounts of [125 I]MIP1 α (0-8.5 nM) to membranes and beads in concentrations chosen from the optimal protein/bead ratio. The data was analyzed using a non-linear curve-fitting program. The K_d and B_{max} were derived from the curve.

Bacitracin 50 mg/ml was dissolved in deionized water, brought to a boil for 5 minutes (to destroy protease activity) and cooled. One milliliter aliquots were prepared and stored at -80°C .

Protease inhibitor cocktail was prepared by dissolving 25 mg/ml of Pefabloc, 1 mg/ml of Leupeptin, 1 mg/ml of Aprotinin and 1 mg/ml of Pepstatin A in 100% DMSO. The cocktail could be aliquoted and stored frozen at -20°C until needed.

Any reagent bottles and reservoirs that come in contact with the radioligand were treated with Sigmacote to reduce sticking. Containers were rinsed with undiluted Sigmacote and with deionized water for several times and allowed to air dry before using.

Color quench assay was performed with a [125 I] SPA PVT color quench kit (Cat. No. RPAQ 4030, Amersham Ltd.). A color quench curve was generated for each Packard TopCount and was stored in each counting protocol specific for the assay. This was done to prevent colored compounds from quenching the scintillation counts.

Compounds of this invention were prepared for SPA according to the following protocol. Compounds for a single concentration determination (one shots) were delivered in 96 well Packard Optiplates containing 1 μl of compound in 100% DMSO in columns A1-H10 (80 compounds/plate). Column A11 to H11 was used for total binding (Bo: zero standard - bound radioactive counts in the absence of added inhibitor or test compound) (vehicle-5 μl of the appropriate DMSO concentration) and column A12 to D12

was used for determination of nonspecific binding (NSB). No further preparation was required. Compounds for concentration-response curves (10 points) were delivered in 96- Packard Optiplates containing 1 μ l of compound in 100% DMSO in columns A1-H10. A 10-point concentration-response curve was desired for each compound with a starting high concentration of 30 μ M (in the assay final). Column A11 to H11 was used for total binding (Bo) (vehicle-5 μ l of the appropriate DMSO concentration) and column A12 to D12 was used for determination of nonspecific binding. No further preparation was required.

Assay buffer was prepared by mixing 50 mM HEPES buffer (pH 7.4), 1 mM CaCl_2 , 5 mM MgCl_2 which could be made ahead as a 100X stock, 1% BSA (bovine serum albumin), 0.5 mg/ml Bacitracin, and protease inhibitor cocktail (100 μ L/100 ml). DMSO was added to equal a final concentration of 2% per well (includes compound %DMSO) if needed.

$[^{125}\text{I}]\text{MIP1}\alpha$ radioligand dilutions was prepared in containers treated with Sigmacote. Each 50 μ Ci vial was reconstituted with 0.5 ml of deionized water and stored at 4°C. The specific activity was 2,000 Ci/mmol. 50 μ L (~60,000 cpm; 0.17 nM) of $[^{125}\text{I}]\text{MIP1}\alpha$ was added to each assay well.

Zero standard (Bo) was prepared by making a 20% DMSO solution and adding 5 μ l of 20% DMSO solution to each well in columns A11-H11. This gave a final 2% DMSO concentration for the well when added to the 1% in the assay buffer.

A stock dilution of $\text{MIP1}\alpha$ at 100 μ M was made using deionized water and aliquoted and frozen. The $\text{MIP-1}\alpha$ stock solution was diluted to a concentration of 2 μ M in the same 20% DMSO solution used above. 5 μ l of the resultant solution was added to the wells in column A12 to D12 to give a final assay concentration of 100 nM. This procedure was conducted in a Sigmacote-treated container.

The final assay concentration for the membrane was 15 μ g per well. SPA beads were prepared by adding 5 ml of assay buffer to a 500 mg vial. The final concentration of SPA beads in the assay was 0.25 mg/well.

Membranes and beads were premixed as a 1:1 (membrane:bead) mixture and maintained at mixture at 4°C with constant stirring. 50 µl of the mixture was added to each assay well. After all reagents had been added to the plates (total assay volume 100 µl), plates were shaken for 4 hours at room temperature. After 4 hours, the plates were placed on the TopCount in a count the plates on the TopCount for 30 sec per well using an appropriate program (i.e., one with a quench curve established for the conditions of the assay).

Data reduction was performed using the Microsoft Excel Addins Robofit or Robosage. For single concentration assays (one shots), the result of each test well was expressed as % inhibition using the following formula: $100 \times (1 - (U1 - C2) / (C1 - C2))$, where U1 was the unknown sample in cpm observed in a particular well, C1 was the average of column 12 cpm observed in the absence of any added inhibitor, and C2 was the average of column 11 cpm observed in the presence of 1 µM of MIP1α. For concentration-response assays, the result of each test well was expressed as %B/Bo (% total specific binding) using the following formula: $100 \times (U1 - C2) / C1 - C2$. Curves were generated by plotting the %B/Bo versus the concentration and the IC₅₀ was derived using the equation $y = V_{max} \times (1 - (x^n / (k^n + x^n)))$.

For controls and standards, each plate contained 12 wells of total binding (column A11-H11). The cpm/well were averaged and used in data reduction as value C1. Each plate also contained 4 wells of non-specific binding (wells A12-D12). The counts of these wells were averaged and used in data reduction as value C2. A standards plate was included in each experiment. This plate contained a 14-point concentration-response curve (in triplicate) for the standard compound MIP1α at a starting concentration of 1 µM. The average historical pK_i obtained with MIP1α was 7.6.

The relevant biological response field for a single concentration (one shots) was % inhibition. Inhibition values of >40 or >50% were considered positive responses. The relevant biological response field for a concentration-response experiment was pK_i.

HOS Assay (Also referred to as HOS-LTR-Luciferase Assay)

HOS-CD4.CCR5-LTR-Luciferase (Bioresource Registration # 21164): Human Osteosarcoma cell line was engineered to overexpress human CD4 and human CCR5 (AIDS Repository cat# 3318) stably transfected with HIV-1-LTR-Luciferase reporter.

Growth and Maintenance of the HOS-CD4.CCR5-LTR-Luciferase cell line: The cells were propagated in DMEM containing 2% FBS. Cells were split by standard trypsinization when confluency reached 80% (roughly every 2 to 3 days).

Titering of virus stocks: HIV-1 virus stocks were titered in the assay system in order to obtain an estimate of the number of infectious particles per unit volume (described as RLU/ml). Virus stocks were diluted into DMEM containing 2% FBS and assayed as described in the "procedure" section below.

Procedure: Black-walled 96-well tissue culture plates were seeded with HOS-CD4.CCR5-LTR-Luciferase @ 0.6 to 1.2×10^3 cells per well in 50 μ l DMEM containing 2% FBS and placed in a humidified incubator @ 37°C, 5% CO₂ overnight. The following day, test compounds were titrated 4-fold at 2X the final concentration in DMEM + 2% FBS + 0.2% DMSO. 50 μ l of titrated compound was transferred to the HOS cells and the plates were placed in a humidified incubator at 37°C, 5% CO₂ for 1 hr. An additional 60 μ l of 2X titrated compound was transferred to a clear-walled 96-well tissue culture plate and 60 μ l of HIV (diluted to appropriate m.o.i.) was added to each well and thoroughly mixed. 100 μ l of the HIV/compound mixture was transferred to the black-walled plates containing 100 μ l of cells/compound. The plates were placed in a humidified incubator at 37°C, 5% CO₂ for 72hr. Following the 72 hour incubation, 150 μ l of supernatant was removed and 50 μ l of reconstituted LUCITE (kit reagent) was added to each well. Each plate was sealed and read in a Topcount (Packard) luminometer at 1s/well.

Data Reduction: Relative Light Units (RLU) were expressed as % control (RLU at drug concentration / RLU no drug)*100 = % Control. IC₅₀

values were determined by any one of the following four nonlinear regression models:

$$y = V_{\max} * (1 - (x^n / (K^n + x^n))) + Y_2;$$

$$y = V_{\max} * (1 - (x^n / (K^n + x^n)));$$

$$y = V_{\max} * (1 - (x / (K + x))) + Y_2;$$

$$y = V_{\max} * (1 - (x / (K + x)));$$

where K is IC_{50} , Y_2 is baseline, and N is Hill Coefficient.

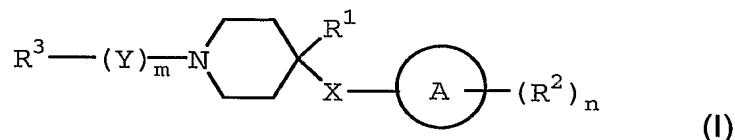
Each of the compounds of the present invention provides a pIC_{50} value of at least 5 when tested in each of the above-described assays.

Test compounds are employed in free or salt form.

While we have hereinbefore presented a number of embodiments of this invention, it is apparent that our basic construction can be altered to provide other embodiments which utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of the invention is to be defined by the appended claims rather than by the specific embodiments which have been represented by way of example.

What is Claimed is:

1. A compound of formula (I):



or a pharmaceutically acceptable derivative thereof, wherein:

R^1 is alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl, wherein said alkyl is optionally substituted by one or more R^7 , said carbocyclyl or heterocyclyl is optionally substituted by one or more R^8 and said aryl or heteroaryl is optionally substituted by one or more R^6 ; or R^1 and X taken together form a saturated, partially saturated or aromatic 5-7 membered ring, having 0-3 heteroatoms chosen from oxygen, sulfur, nitrogen and phosphorus, that is fused to Ring A;

X is a C_{1-5} alkylene chain, wherein said C_{1-5} alkylene chain is optionally substituted by one or more groups chosen from =O, =S and halo, and wherein said C_{1-5} alkylene chain optionally contains 1-3 heteroatoms chosen from oxygen, sulfur, nitrogen and phosphorus;

Ring A is a saturated, partially saturated or aromatic 5-6 membered monocyclic or 8-10 membered bicyclic ring having 0-5 ring heteroatoms chosen from oxygen, sulfur and nitrogen;

each R^2 is independently chosen from $-OR^0$, $-C(O)R^0$, $-C(O)N(R^0)_2$, $-N(R^0)(-V_m-R^+)$, $-S(O)_2-R^0$, $-S(O)_2-N(R^0)_2$, $-(CH_2)_a-N(R^0)(-V_b-R^+)$, $-(CH_2)_a-(-V_b-R^+)$, halo, alkyl, aryl, carbocyclyl, heteroaryl and heterocyclyl, wherein said alkyl is optionally substituted by one or more R^7 , said aryl or heteroaryl is optionally substituted by one or more R^6 , and said carbocyclyl or heterocyclyl is optionally substituted by one or more R^8 ; or two adjacent R^2 s on Ring A are optionally taken together to form a fused, saturated, partially saturated or aromatic 4-7 membered ring having 0-3 heteroatoms chosen from oxygen, sulfur, nitrogen and phosphorus; or two geminal R^2 s are optionally taken together to form a spiro, saturated, partially saturated or

aromatic 5-6 membered ring having 0-3 heteroatoms chosen from oxygen, sulfur and nitrogen, said fused or spiro ring being optionally substituted by one or more groups chosen from oxo, alkyl optionally substituted by one or more R^7 , and aryl optionally substituted by one or more R^6 ;

each a is independently 0-3;

each b is independently 0 or 1;

V is alkyl, $-C(O)-$, $-S(O)_2-$, $-C(O)O-$, or $-C(O)-N(R^0)-$ (when V is attached to R^+ through the right hand side of the radical;

R^+ is alkyl, aralkyl, aryl, heteroaryl, heteroaralkyl, wherein said alkyl is optionally substituted by one or more R^7 and said aralkyl or aryl is optionally substituted by one or more R^6 ;

m is 0 or 1;

n is 0-5;

R^3 is H, halo, $-N(R^0)_2$, $-N(R^0)C(O)R^0$, $-CN$, $-CF_3$, alkyl optionally substituted by one or more groups chosen from R^7 and $-S$ -aryl optionally substituted by $-(CH_2)_{1-6}-N(R^0)SO_2(R^0)$, carbocyclyl, aryl, heteroaryl or heterocyclyl, wherein said carbocyclyl or heterocyclyl is optionally substituted by one or more R^8 , and said aryl or heteroaryl is optionally substituted by one or more R^6 ;

Y is $-(CR^4R^5)_p-$, $-C(O)-$, $-C(O)C(O)-$, $-C(S)-$, $-O-(CH_2)_{0-4}-C(O)-$, $-N(R^0)-C(O)-$, $-C(O)-N(R^0)-$, $-N(R^0)-C(S)-$, $-S(O)_t-$, $-O-C(=N-CN)-$, $-O-C(=N-R^0)-$, $-S-C(=N-CN)-$, $-N(R^0)-C(=N-CN)-$, $-C(=N-CN)-$, $-N(R^0)-C[=N-C(O)-R^0]-$, $-N(R^0)-C[=N-S(O)_t-R^0]-$, $-N(R^0)-C(=N-OR^0)-$, $-N(R^0)-C(=N-R^0)-$, $-C(=N-R^0)-$, $-(CH_2)_{0-4}-C(O)-O-$, $-C(=N-CN)-O-$, $-C(=N-R^0)-O-$, or $-C(=N-CN)-S-$ when Y is attached to R^3 through the left hand side of the radical;

each R^4 is independently H or alkyl optionally substituted by R^7 ;

each R^5 is independently chosen from H, $-C(O)-OR^0$, aryl optionally substituted by R^6 , $-C(O)-OR^6$, $-C(O)-N(R^0)_2$, $-S(O)_2-N(R^0)_2$, $-S(O)_2-R^0$, and heteroaryl optionally substituted by R^6 ;

p is 1-5;

t is 1 or 2;

each R^6 is independently chosen from halo, $-CF_3$, $-OCF_3$, $-OR^0$, $-SR^0$, $-SCF_3$, $-R^0$, methylenedioxy, ethylenedioxy, $-NO_2$, $-CN$, $-N(R^0)_2$, $-NR^0C(O)R^0$, $-NR^0C(O)N(R^0)_2$, $-NR^0C(S)N(R^0)_2$, $-NR^0CO_2R^0$, $-NR^0NR^0C(O)R^0$, $-NR^0NR^0C(O)N(R^0)_2$, $-NR^0NR^0CO_2R^0$, $-C(O)C(O)R^0$, $-C(O)CH_2C(O)R^0$, $-CO_2R^0$, $-O-C(O)R^0$, $-C(O)R^0$, $-C(O)N(R^0)_2$, $-OC(O)N(R^0)_2$, $-S(O)_tR^0$, $-S(O)_t-OR^0$, $-SO_2N(R^0)C(O)R^0$, $-NR^0SO_2N(R^0)_2$, $-NR^0SO_2R^0$, $-C(=S)N(R^0)_2$, $-C(=NH)-N(R^0)_2$, $-C(=N-OR^0)-N(R^0)_2$, $-O-(CH_2)_{0-6}-SO_2N(R^0)_2$, $-(CH_2)_{1-6}NHC(O)R^0$, $-SO_2N(R^0)_2$, $-(CH_2)_{1-6}-OR^0$, $-(CH_2)_{1-6}-SR^0$, $-(CH_2)_{1-6}-CN$, $-(CH_2)_{1-6}-N(R^0)_2$, $-(CH_2)_{1-6}CO_2R^0$, $-C(O)N(R^0)N(R^0)_2$, $-C(O)N(R^0)OH$, $-C(O)N(R^0)SO_2R^0$, $-S(O)_tN(R^0)OR$, and $-(CH_2)_{1-6}-C(O)R^0$, wherein the two R^0 s on the same nitrogen optionally taken together forming a 5-8 membered saturated, partially saturated or aromatic ring having additional 0-4 ring heteroatoms chosen from oxygen, nitrogen, sulfur and phosphorus;

each R^7 is independently chosen from halogen, $-CF_3$, $-R^0$, $-OR^0$, $-SR^0$, aryl optionally substituted by R^6 , $-NO_2$, $-CN$, $-N(R^0)_2$, $-NR^0C(O)R^0$, $-NR^0C(O)N(R^0)_2$, $-N(R^0)C(S)N(R^0)_2$, $-NR^0CO_2R^0$, $-NR^0NR^0C(O)R^0$, $-NR^0NR^0C(O)N(R^0)_2$, $-NR^0NR^0CO_2R^0$, $-C(O)C(O)R^0$, $-C(O)CH_2C(O)R^0$, $-CO_2R^0$, $-C(O)R^0$, $-C(O)N(R^0)-N(R^0)_2$, $-C(O)N(R^0)_2$, $-C(O)NR^0SO_2R^0$, $-OC(O)N(R^0)_2$, $-S(O)_tR^0$, $-NR^0SO_2N(R^0)_2$, $-NR^0SO_2R^0$, $-C(=S)N(R^0)_2$, $-C(=NH)-N(R^0)_2$, $-(CH_2)_{1-6}-C(O)R^0$, $-SO_2N(R^0)_2$, $-OCF_3$, $-SCF_3$, $-(CH_2)_{1-6}-SR^0$, methylenedioxy, ethylenedioxy, $-(CH_2)_{1-6}-CN$, $-(CH_2)_{1-6}-N(R^0)_2$, $-S(O)_tN(R^0)OR^0$, $-(CH_2)_{1-6}-C(O)R^0$, $-C(=N-OR^0)-N(R^0)_2$, $-O-(CH_2)_{0-6}-SO_2N(R^0)_2$, and $-(CH_2)_{1-6}-NHC(O)R^0$, wherein the two R^0 s on the same nitrogen optionally taken together form a 5-8 membered saturated, partially saturated or aromatic ring having additional 0-4 ring heteroatoms chosen from oxygen, nitrogen, sulfur and phosphorous;

each R^8 is independently chosen from R^7 , $=O$, $=S$, $=N(R^0)$, and $=N(CN)$;

each R^0 is independently chosen from R^* , $-C(O)$ -aralkyl, $-S(O)_t$ -heteroaryl, carbocyclylalkyl, aralkyl, heteroaralkyl, and heterocyclylalkyl, wherein each member of R^0 except H is optionally substituted by one or more groups chosen from R^* , $-OR^*$, $N(R^*)_2$, $=O$, $=S$, halo, $-CF_3$, $-NO_2$, $-CN$,

-C(O)R*, -CO₂R*, -C(O)-aryl, -C(O)-heteroaryl, -O-aryl, aralkyl, -S(O)_t-aryl, -NR*SO₂R*, -NR*C(O)R*, -NR*C(O)N(R*)₂, -N(R*)C(S)N(R*)₂, -NR*CO₂R*, -NR*NR*C(O)R*, -NR*NR*C(O)N(R*)₂, -NR*NR*CO₂R*, -C(O)C(O)R*, -C(O)CH₂C(O)R*, -C(O)N(R*)N(R*)₂, -C(O)N(R*)₂, -C(O)NR*SO₂R*, -OC(O)N(R*)₂, -S(O)_tR*, -NR*SO₂N(R*)₂, and -SO₂N(R*)₂ wherein the two R*s on the same nitrogen optionally taken together form a 5-8 membered saturated, partially saturated or aromatic ring having additional 0-4 ring heteroatoms chosen from oxygen, nitrogen, sulfur and phosphorus; and each R* is independently H, alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl.

2. The compound according to claim 1 having one or more of the features selected from the group consisting of:

(a) R¹ is alkyl, aryl, heteroaryl or heterocyclyl, wherein said alkyl is optionally substituted by one or more R⁷, said aryl or heteroaryl is optionally substituted by one or more R⁶, and said heterocyclyl is optionally substituted by one or more R⁸;

(b) X is a C₁₋₅ alkylene chain optionally substituted by one or more groups chosen from =O and halo;

(c) Ring A is an 8-10 membered bicyclic ring having 0-5 ring heteroatoms chosen from oxygen, sulfur and nitrogen;

(d) R² is aryl, heteroaryl or heterocyclyl, wherein said aryl or heteroaryl is optionally substituted by one or more R⁶ and said heterocyclyl is optionally substituted by one or more R⁸;

(e) Y is -C(R⁰)[C(O)OR⁰]-, -C(O)-, -O-C(O)-, -N(R⁰)-C(O)-, -S(O)₂-, -O-C(=N-CN)-, -S-C(=N-CN)-, -N(R⁰)-C(=N-CN)-, -C(=N-CN)-, -N(R⁰)-C(S)-, -N(R⁰)-C(=N-OR⁰)-, -N(R⁰)-C[=N-S(O)_t-R⁰], -O-C(=N-R⁰)-, -N(R⁰)-C[=N-C(O)-R⁰], -N(R⁰)-C(=N-R⁰)-, or -C(=N-R⁰)-; wherein each R⁰ is independently R* and m is 1; and

(f) R³ is alkyl, aryl, heteroaryl, heterocyclyl or carbocyclyl, wherein said alkyl is optionally substituted by one or more R⁷, said aryl or

heteroaryl is optionally substituted by one or more R^6 , and said heterocyclyl or carbocyclyl is optionally substituted by one or more R^8 .

3. The compound according to claim 2, wherein:

(a) R^1 is aryl optionally substituted by one or more R^6 ;

(b) X is a C_2 alkylene chain optionally substituted by one or more groups chosen from =O and halo;

(c) Ring A is an 8-9 membered bicyclic ring having one ring nitrogen and 0-4 additional ring heteroatoms chosen from oxygen, sulfur and nitrogen;

(d) R^2 is heteroaryl optionally substituted by one or more R_6 , or heterocyclyl optionally substituted by one or more R_8 ;

(e) Y is $-C(R^0)[C(O)OR^0]-$, $-CH(COOH)-$, $-C(O)-$, $-O-C(O)-$, $S(O)_t-$, $-N(R^0)-C(O)-$, $-O-C(=N-CN)-$, or $-N(R^0)-C(S)-$; wherein each R^0 is independently R^* and m is 1; and

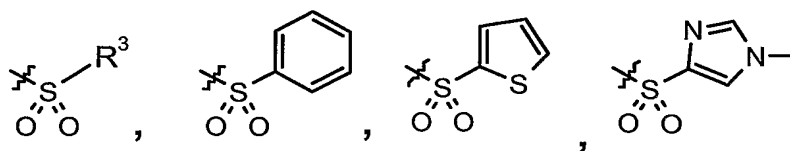
(f) R^3 is alkyl optionally substituted by one or more R^7 , aryl or heteroaryl wherein said aryl or heteroaryl is optionally substituted by one or more R^6 .

4. The compound of claim 1 wherein R^1 is optionally substituted aryl.

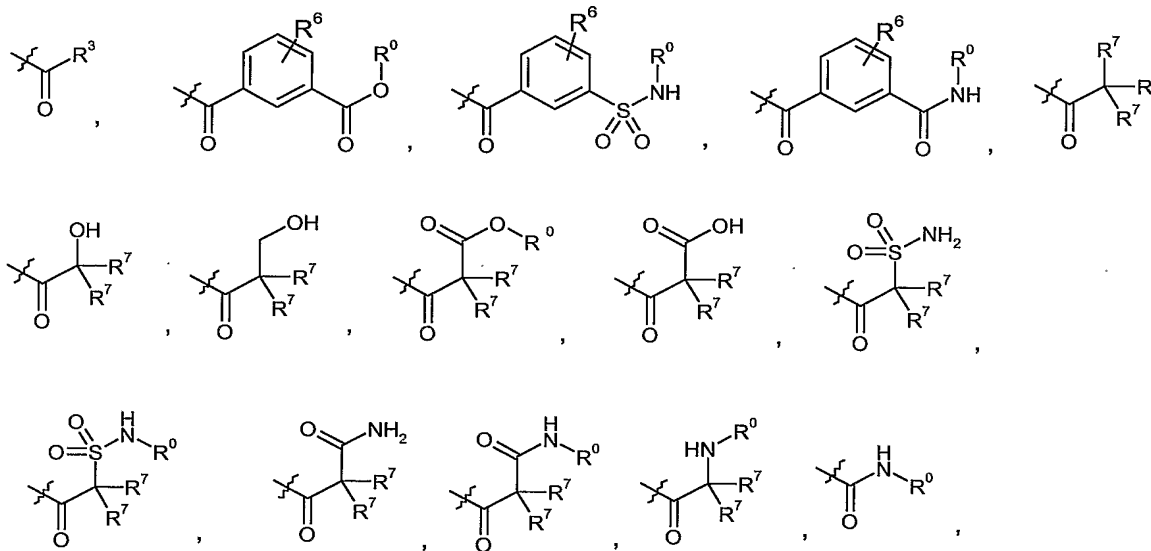
5. The compound of claim 4 wherein R^1 is phenyl mono- or di- substituted with halogen.

6. The compound of claim 5 wherein R^1 is phenyl substituted with F.

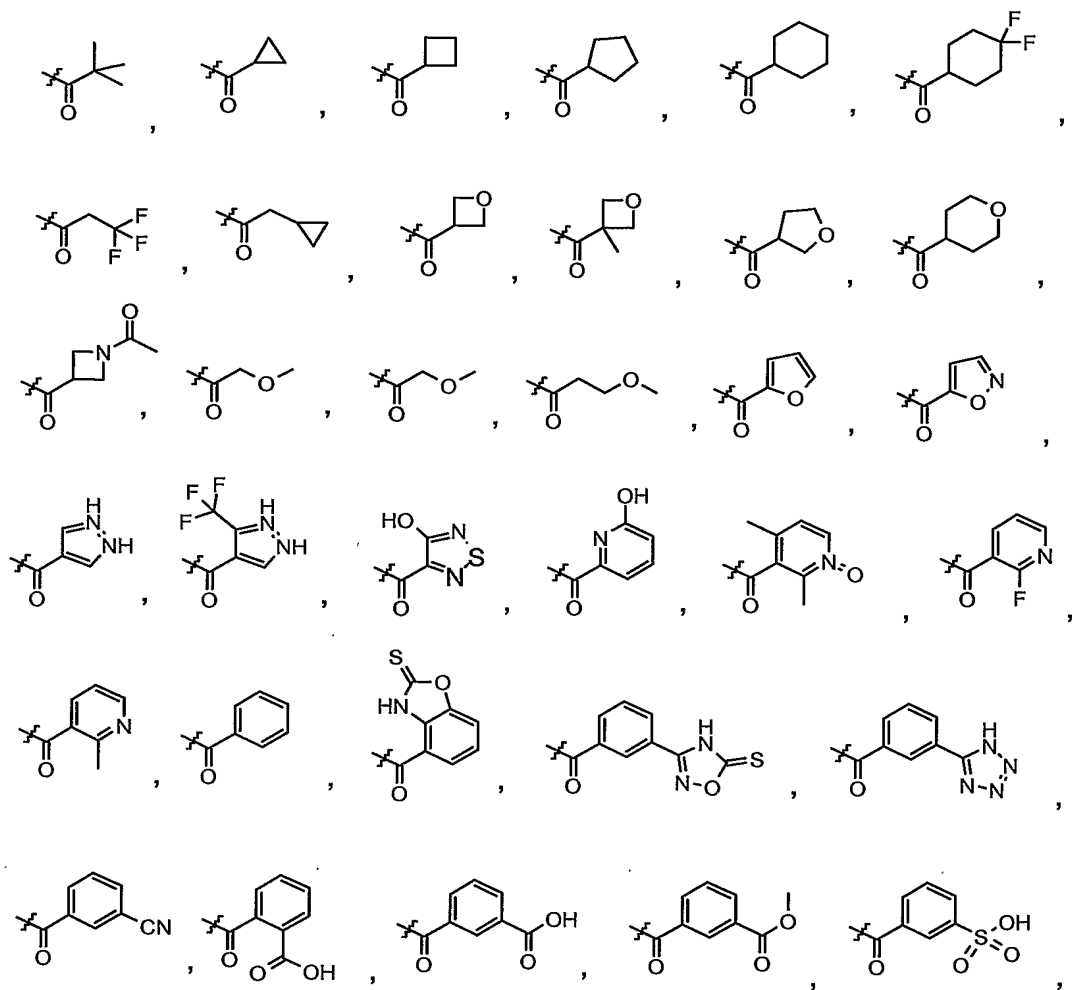
7. The compound of claim 1 wherein m is 1, Y is selected from the group consisting of



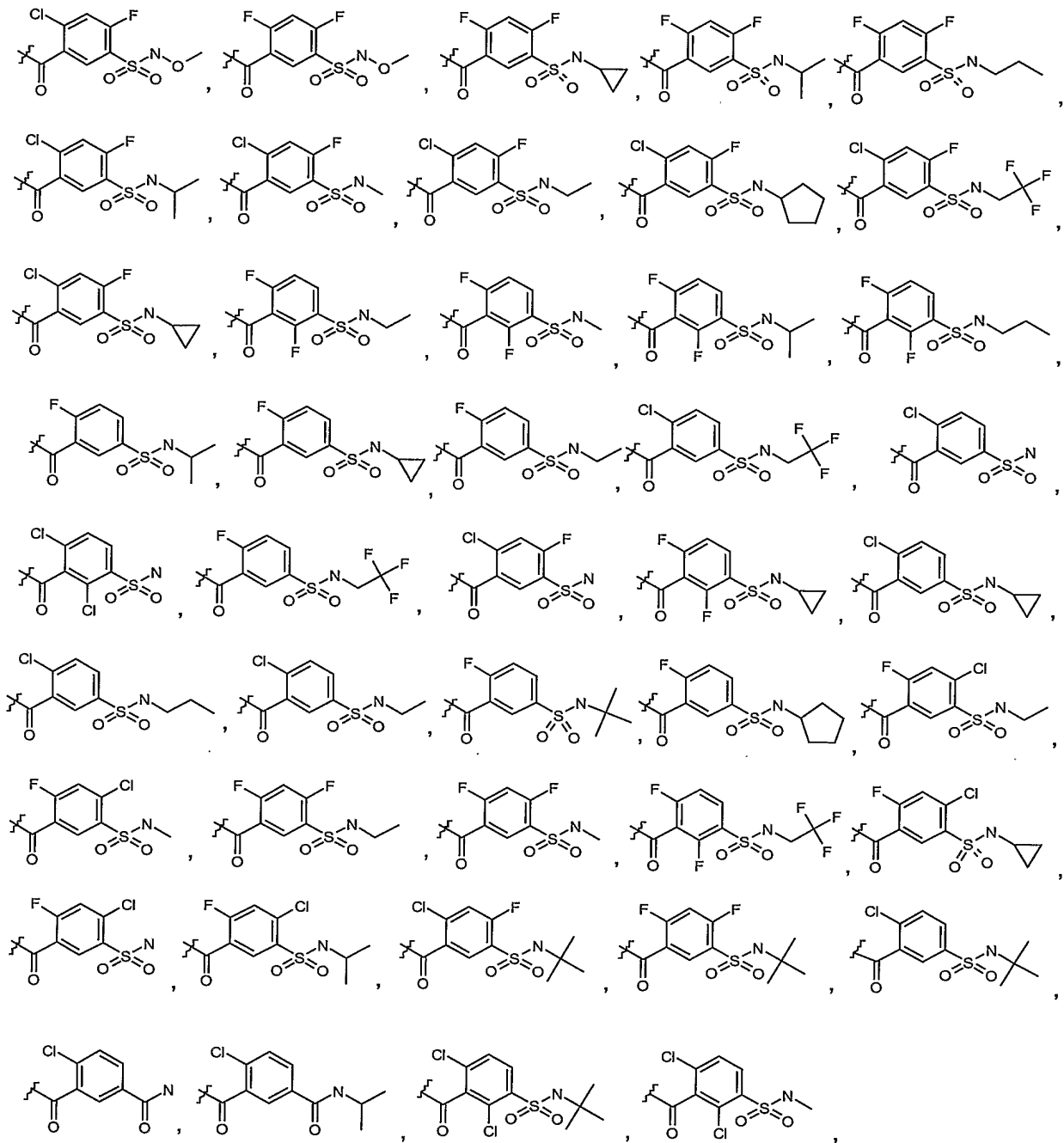
8. The compound of claim 1 wherein m is 1, and Y-R³ selected from the group consisting of



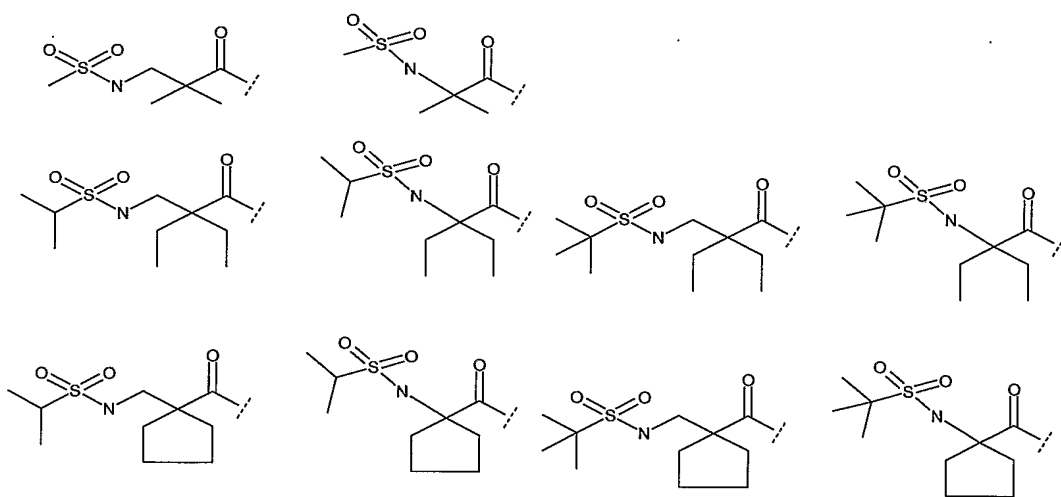
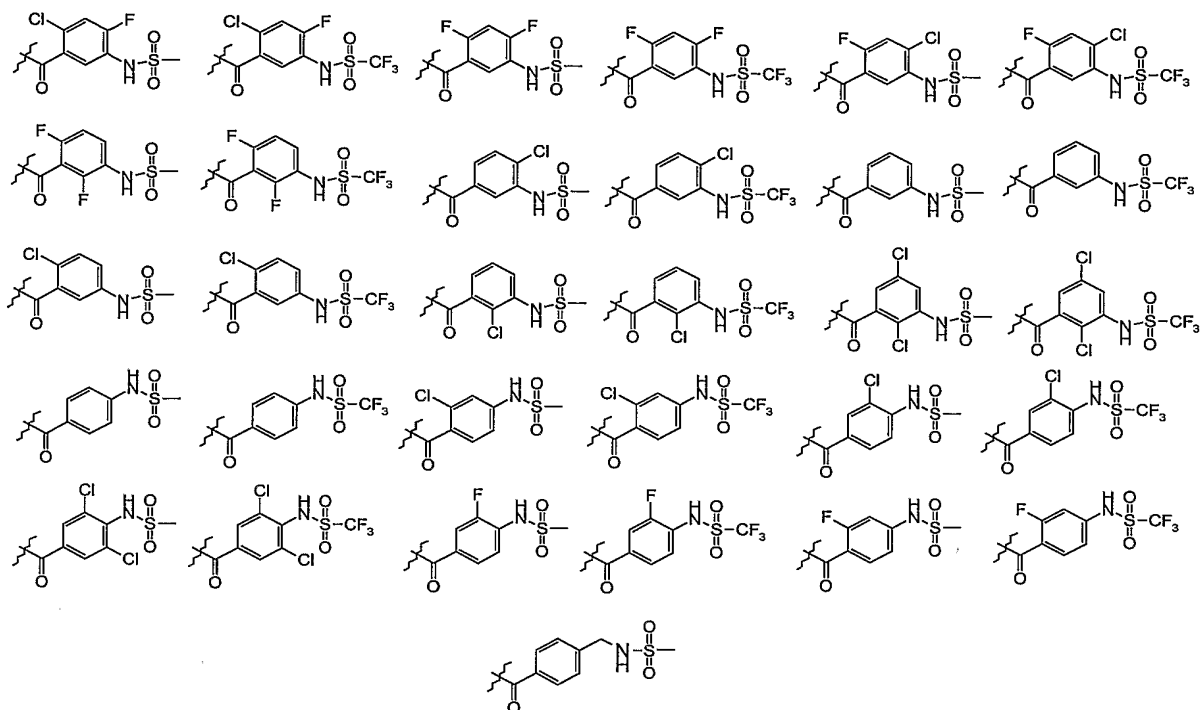
820

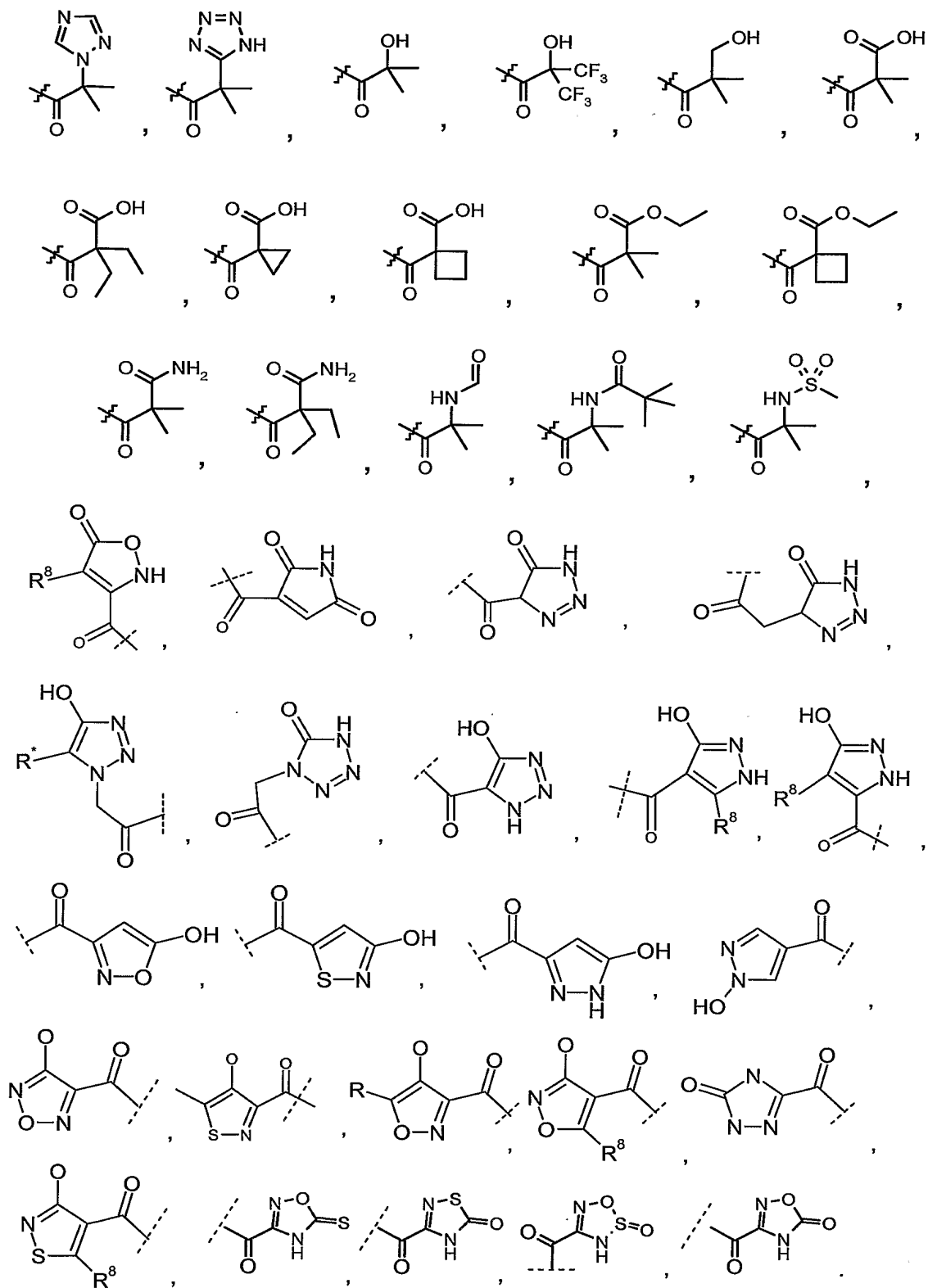


821

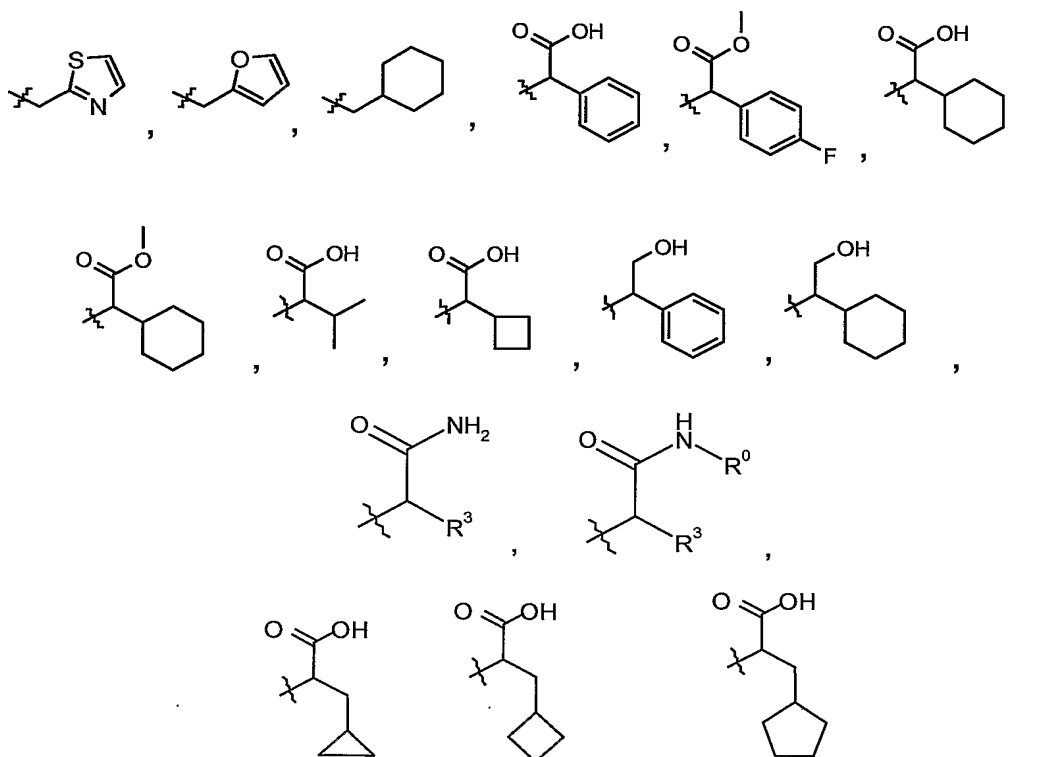


822



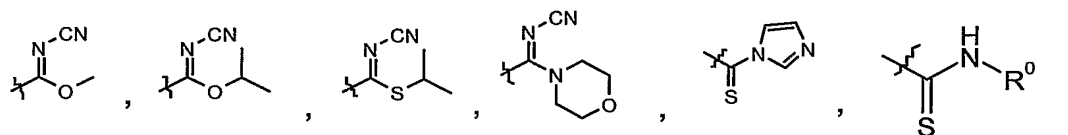


9. The compound of claim 1 wherein m is 1, Y-R³ is selected from the group consisting of



10. The compound of claim 1 wherein m is 0, R³ is directly attached to N, and R³ is optionally substituted aryl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, or optionally substituted heterocyclyl.

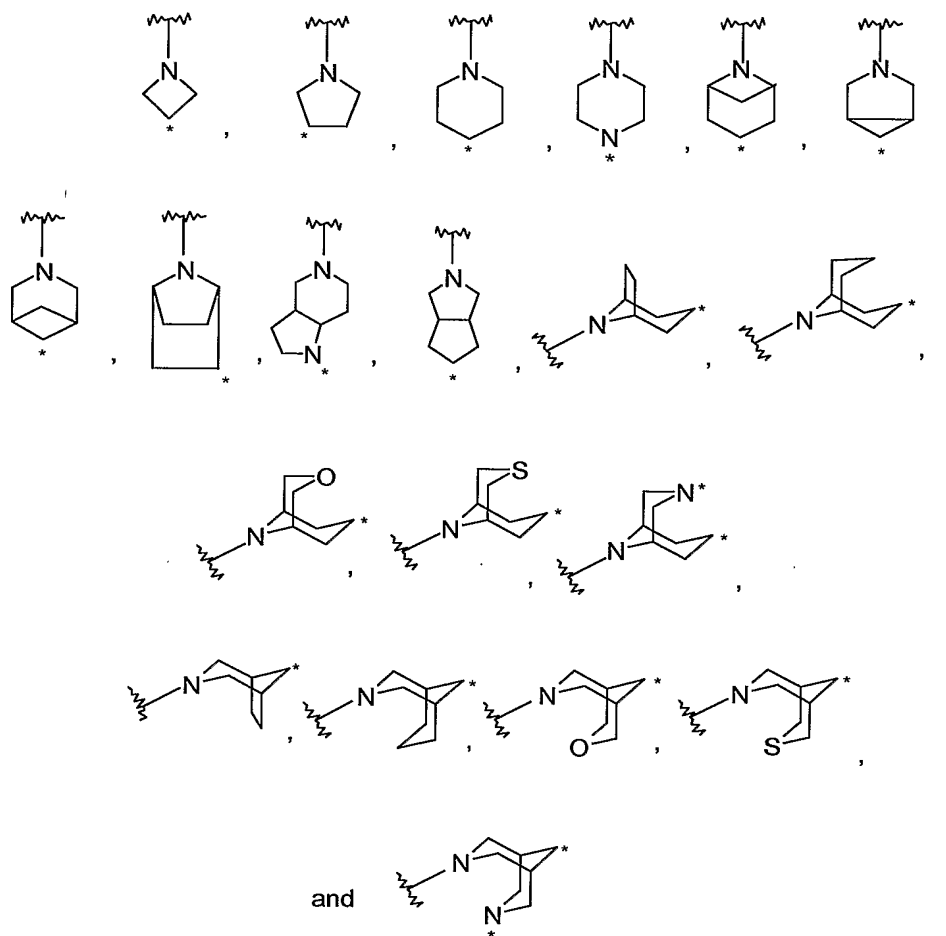
11. The compound of claim 1 wherein m is 1, Y-R³ is selected from the group consisting of



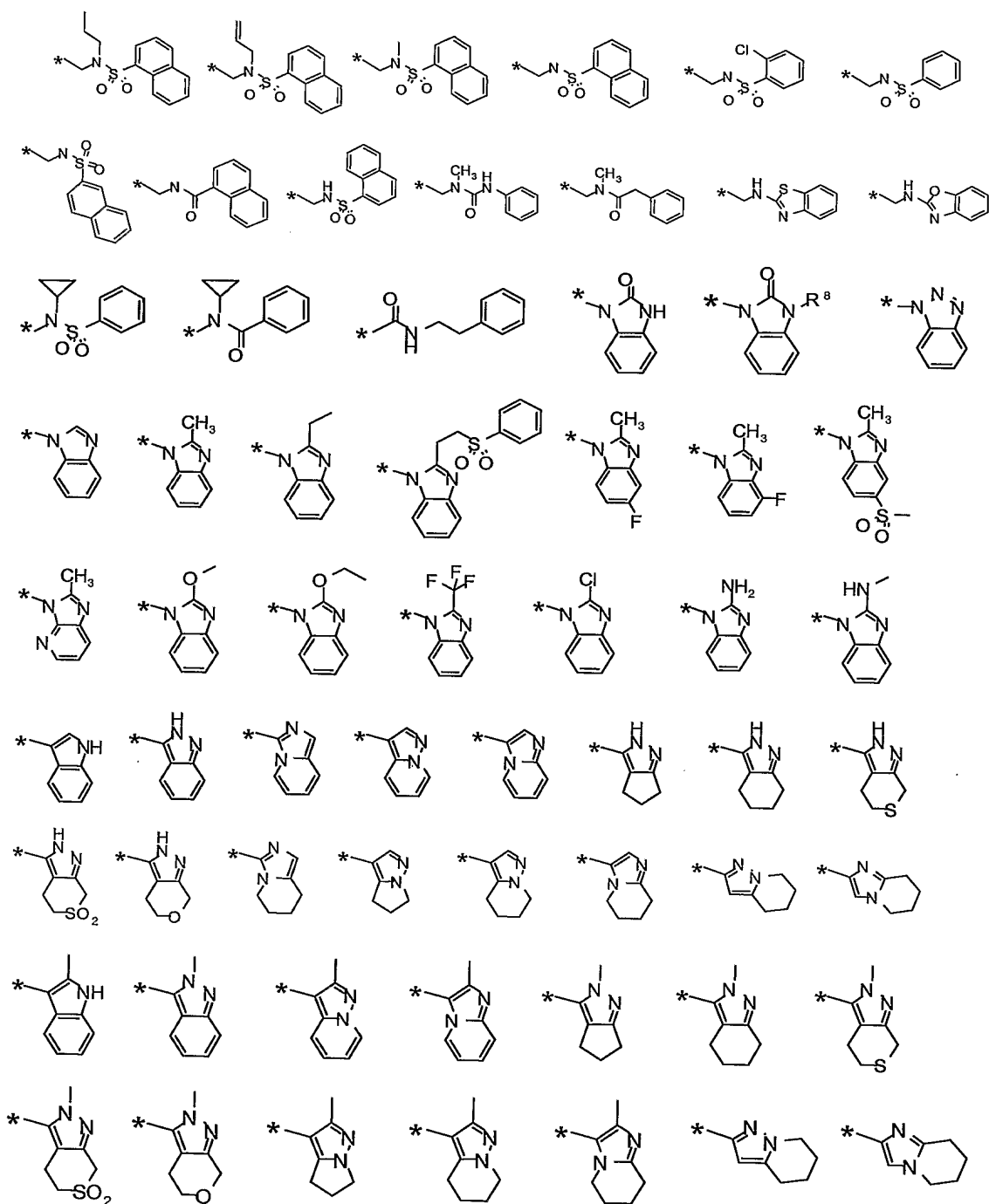
12. The compound of claim 1 wherein m is 1, Y is -C(O)O-, and R³ is optionally substituted alkyl or optionally substituted aryl.

13. The compound of claim 1 where X is $-(CH_2)-$, $-(CH_2-CH_2)-$, or $-(CH_2-CH_2-CH_2)-$.
14. The compound of claim 13 wherein X is optionally substituted by one or more halogen or oxo.
15. The compound of claim 14 wherein X is disubstituted with halogen.
16. The compound of claim 15 wherein X is disubstituted with fluoro.
17. The compound of claim 16 wherein X is $-(CF_2-CH_2)-$.
18. The compound of claim 13 wherein X optionally has 1-3 heteroatoms selected from oxygen, phosphorus, sulfur, and nitrogen.

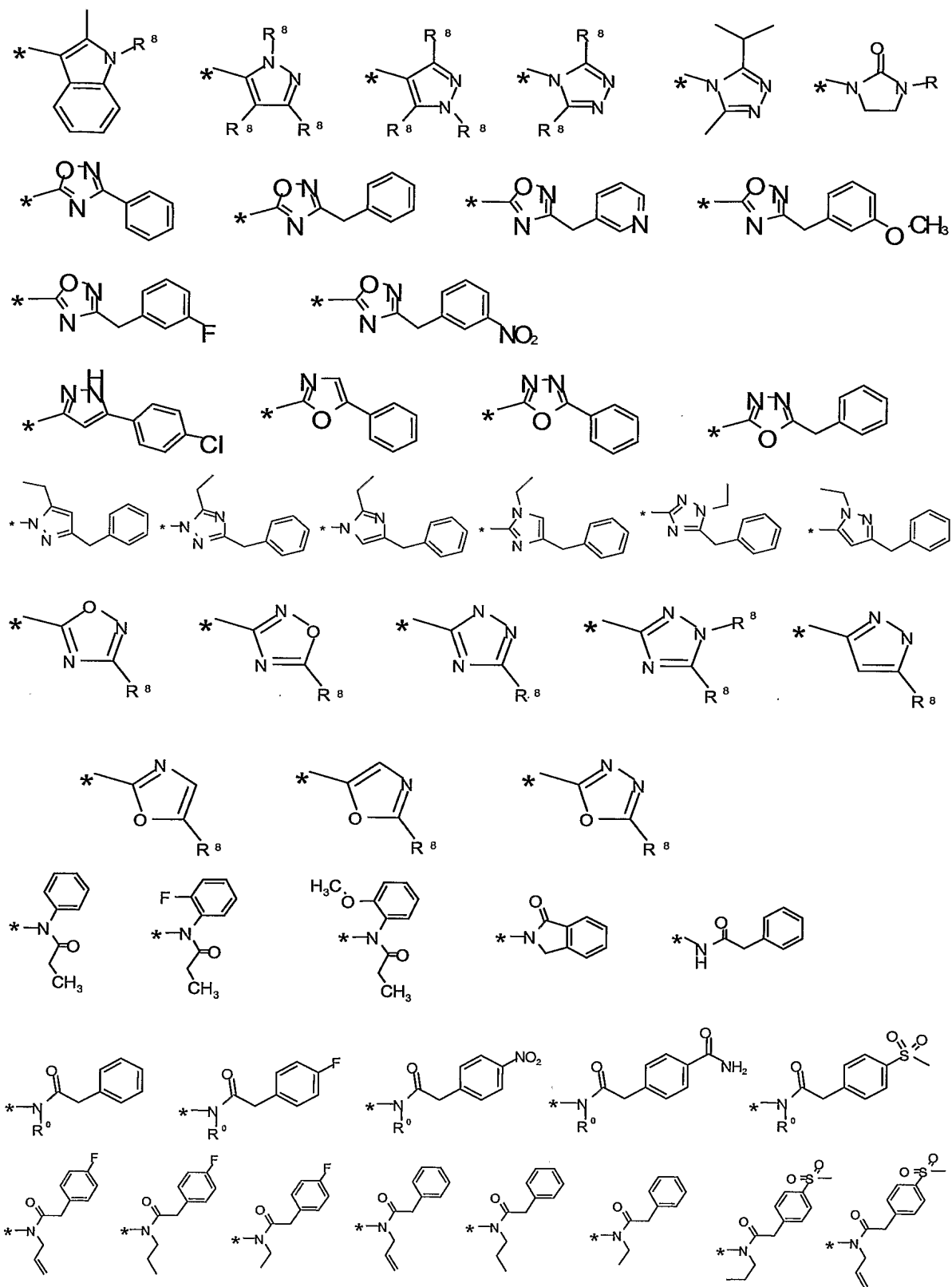
19. The compound of claim 1 wherein the A ring is selected from, where the asterisk (*) indicates the preferred, but not limiting point(s) of substitution,



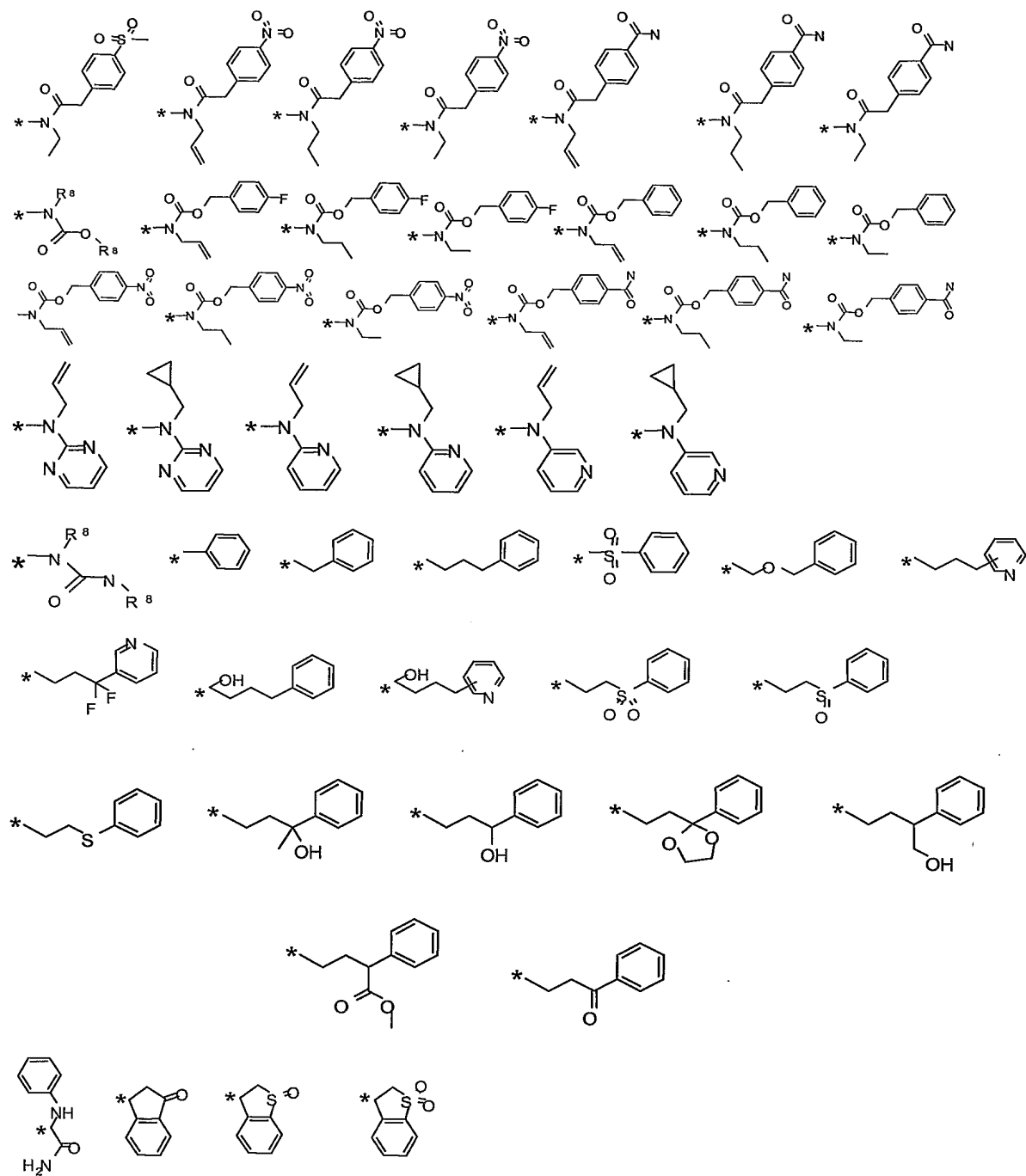
20. The compound of claim 1 wherein each R^2 , with an asterisk indicating a point of substitution from ring A, independently is selected from the group consisting of



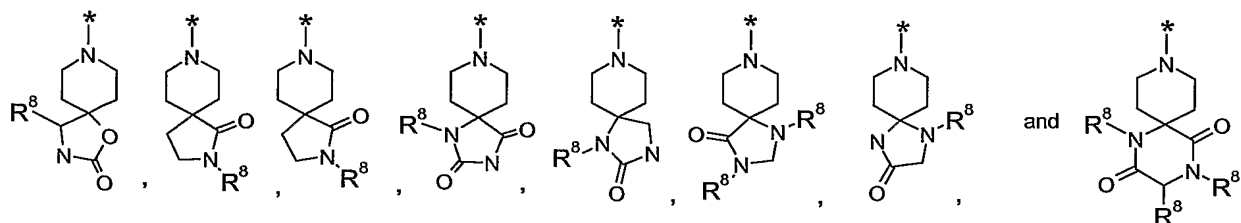
828



829

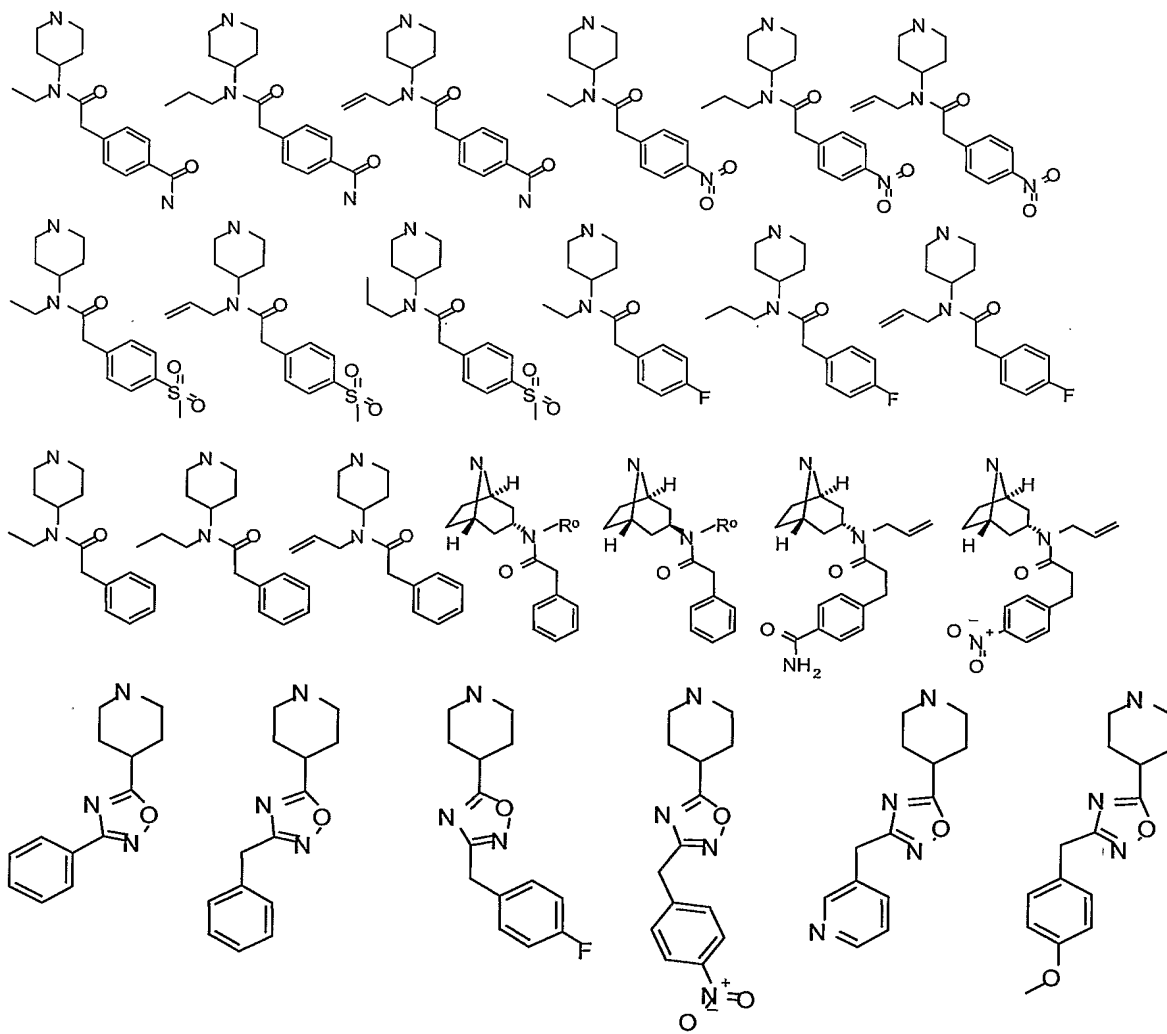


21. The compound of claim 1 wherein the A ring, with two geminal R²s, is selected from the group consisting of

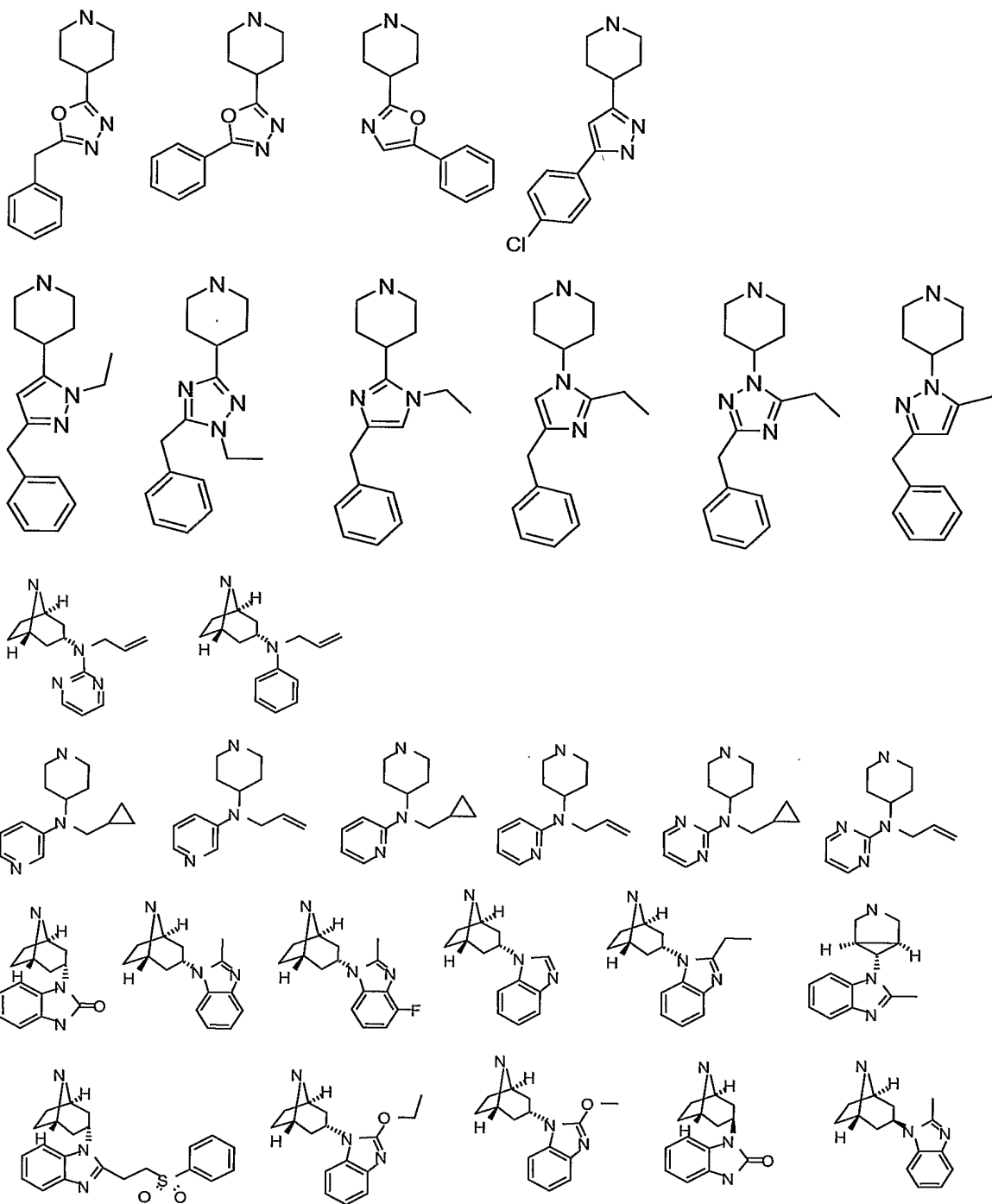


22. The compound of claim 1 wherein the A ring is tropane or piperidine, either optionally substituted with one or more R^2 .

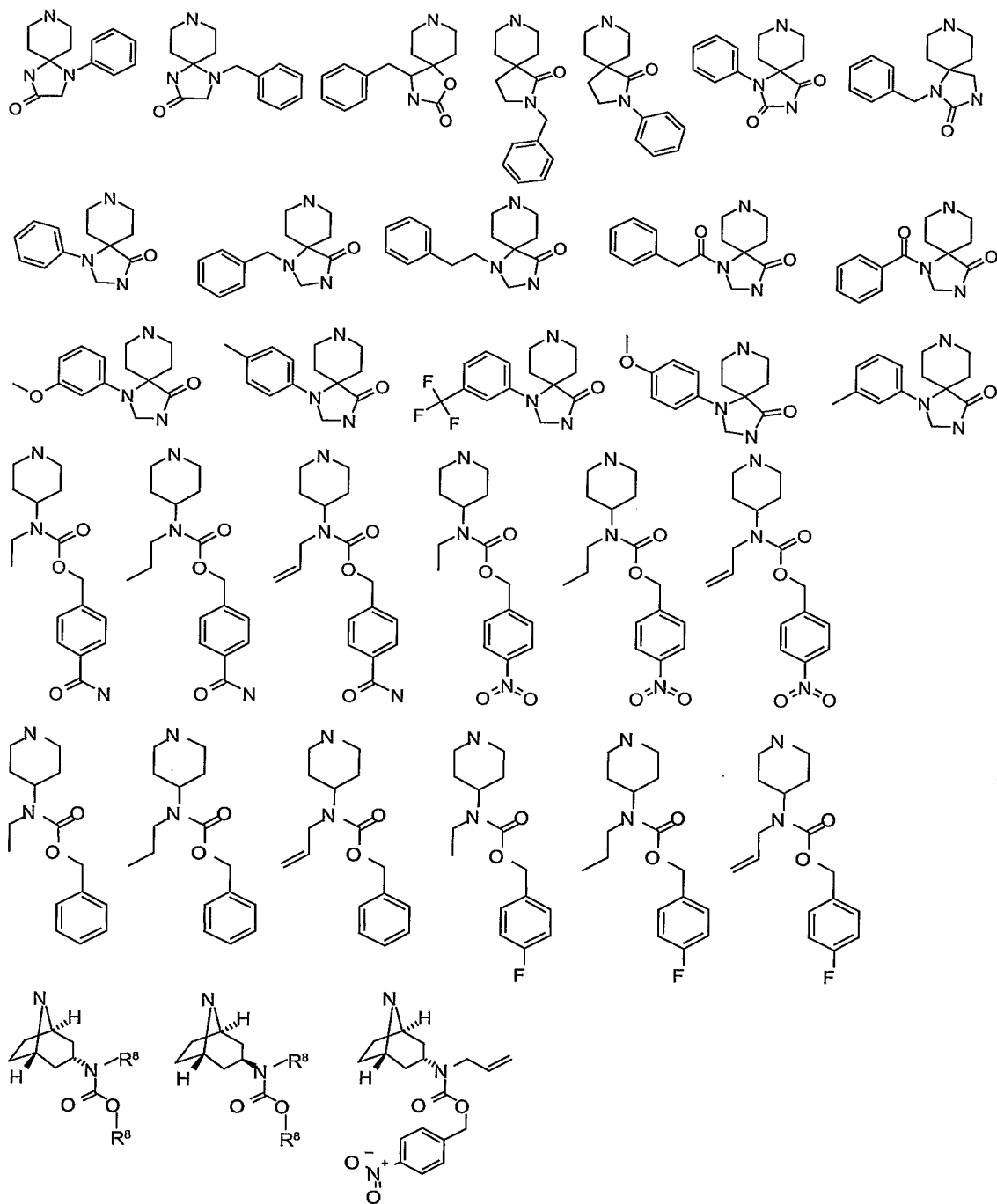
23. The compound of claim 22 wherein the A ring in combination with R^2 is



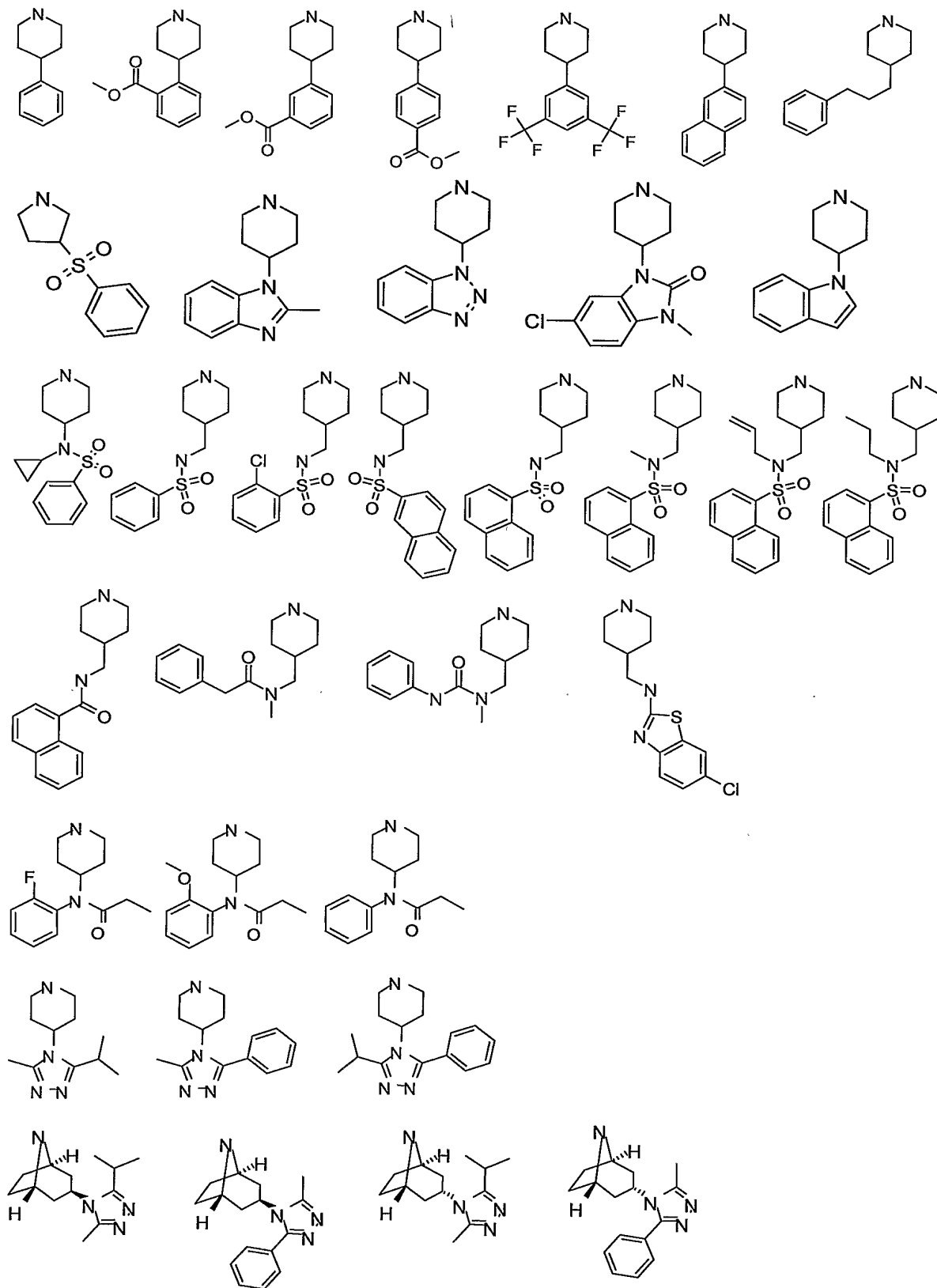
831



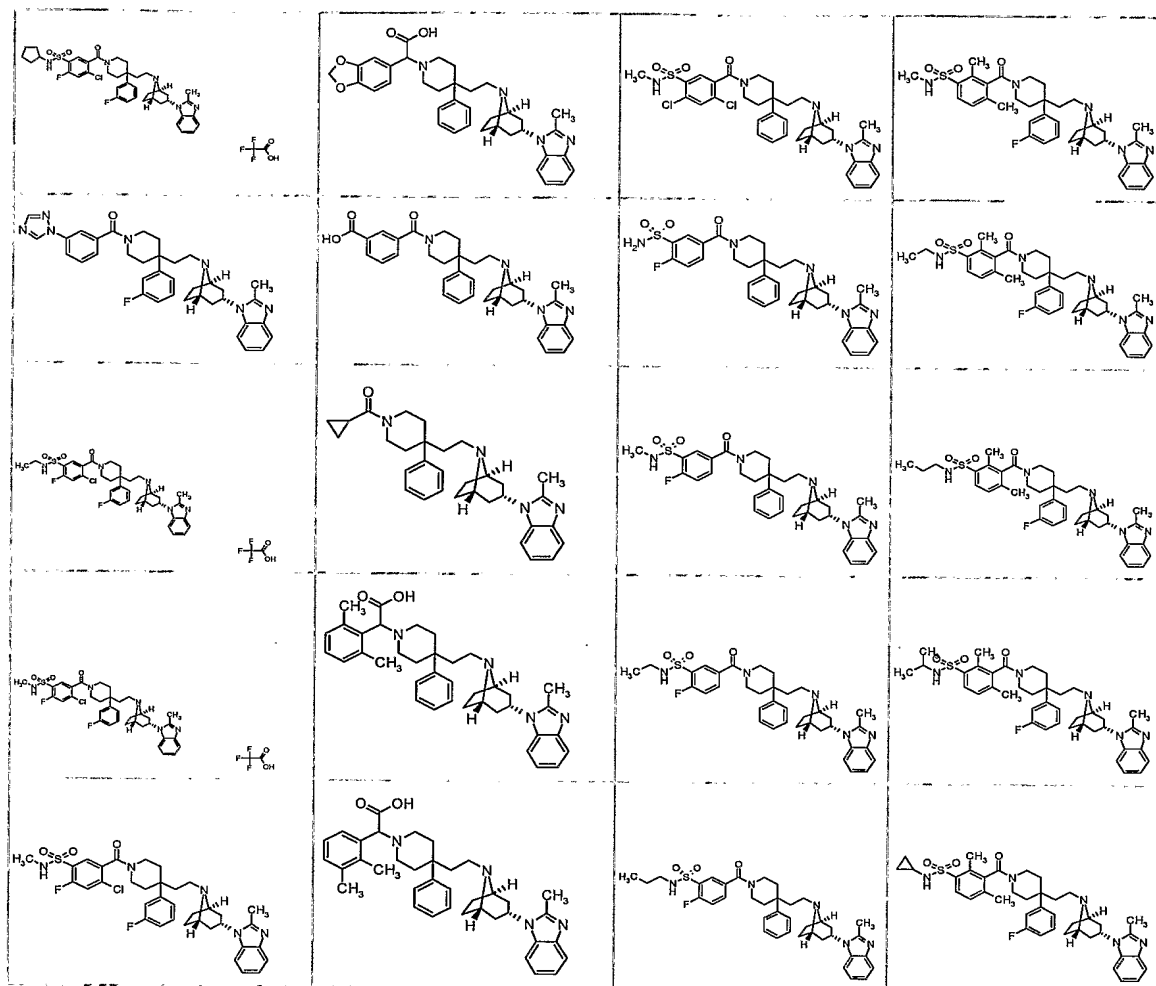
832

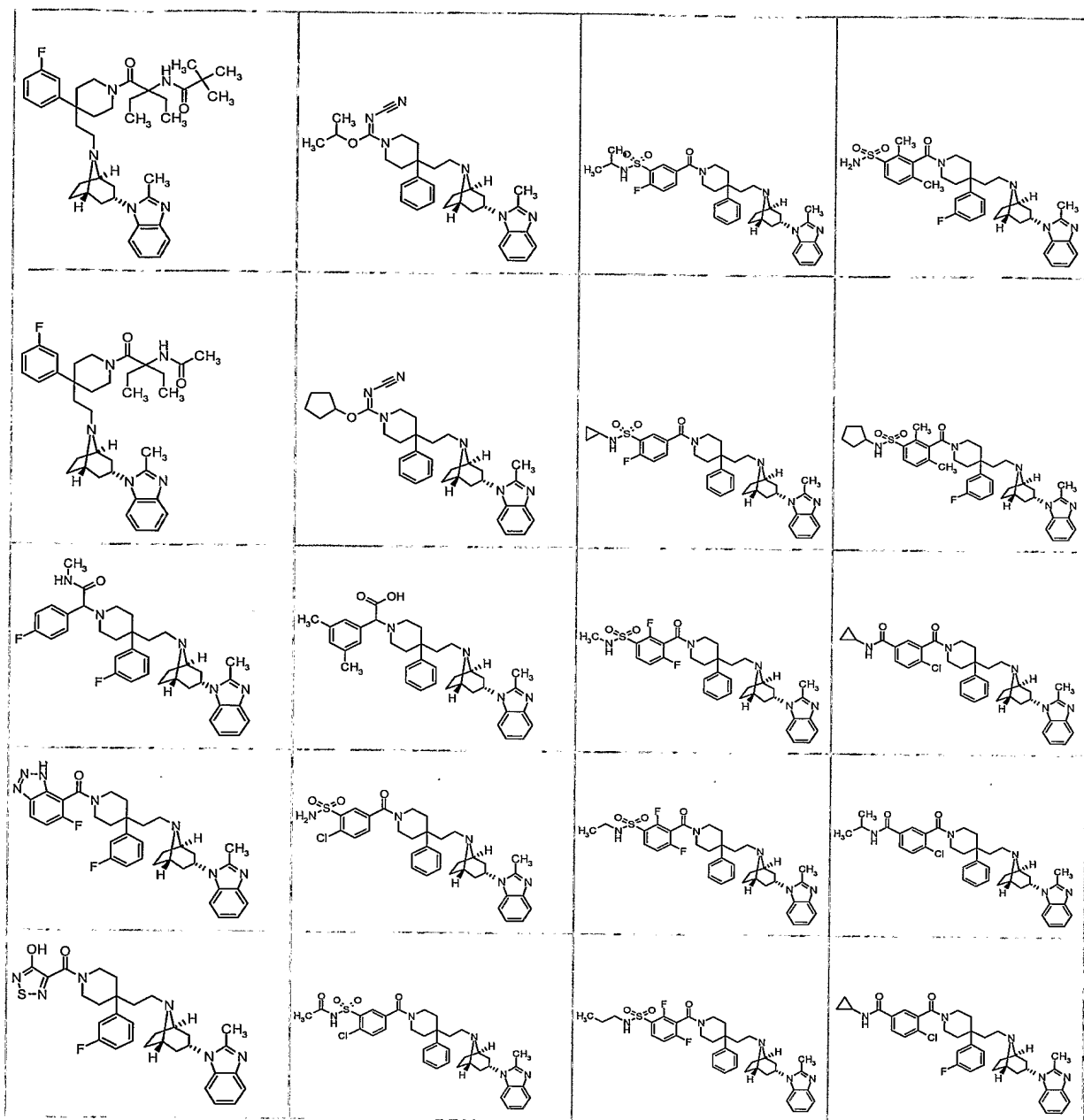


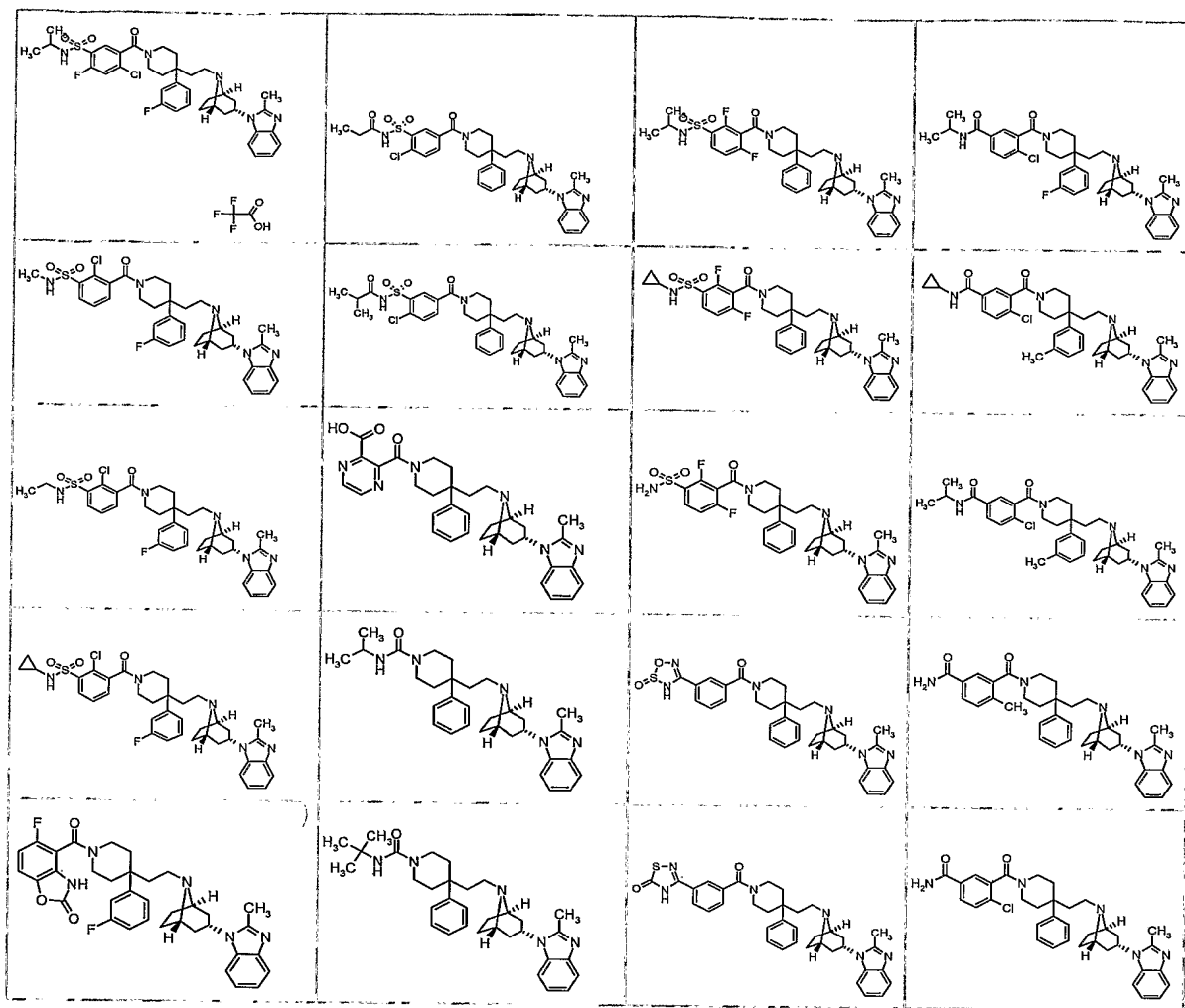
833

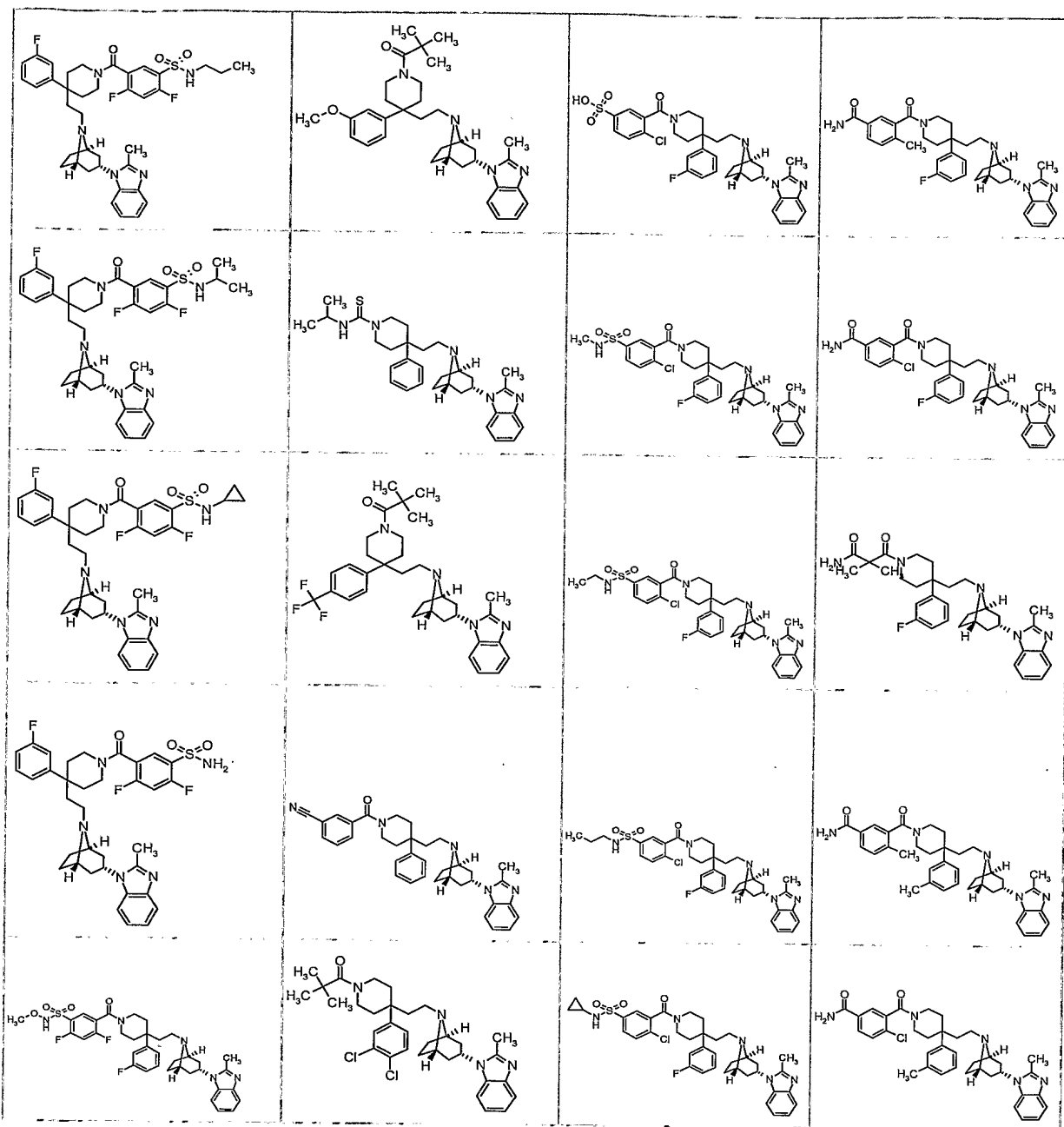


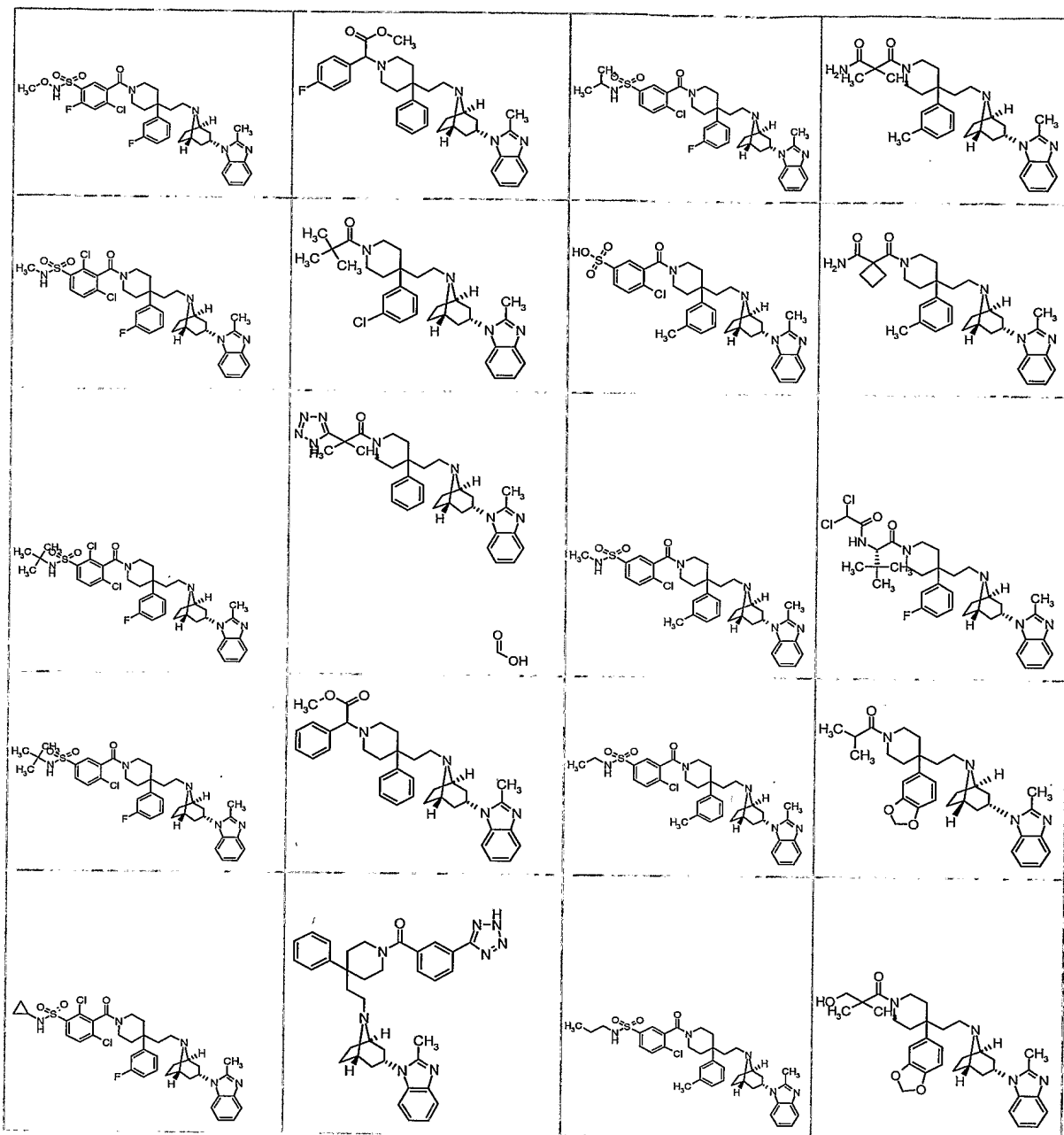
24. The compound according to claim 1 selected from among the group consisting of:

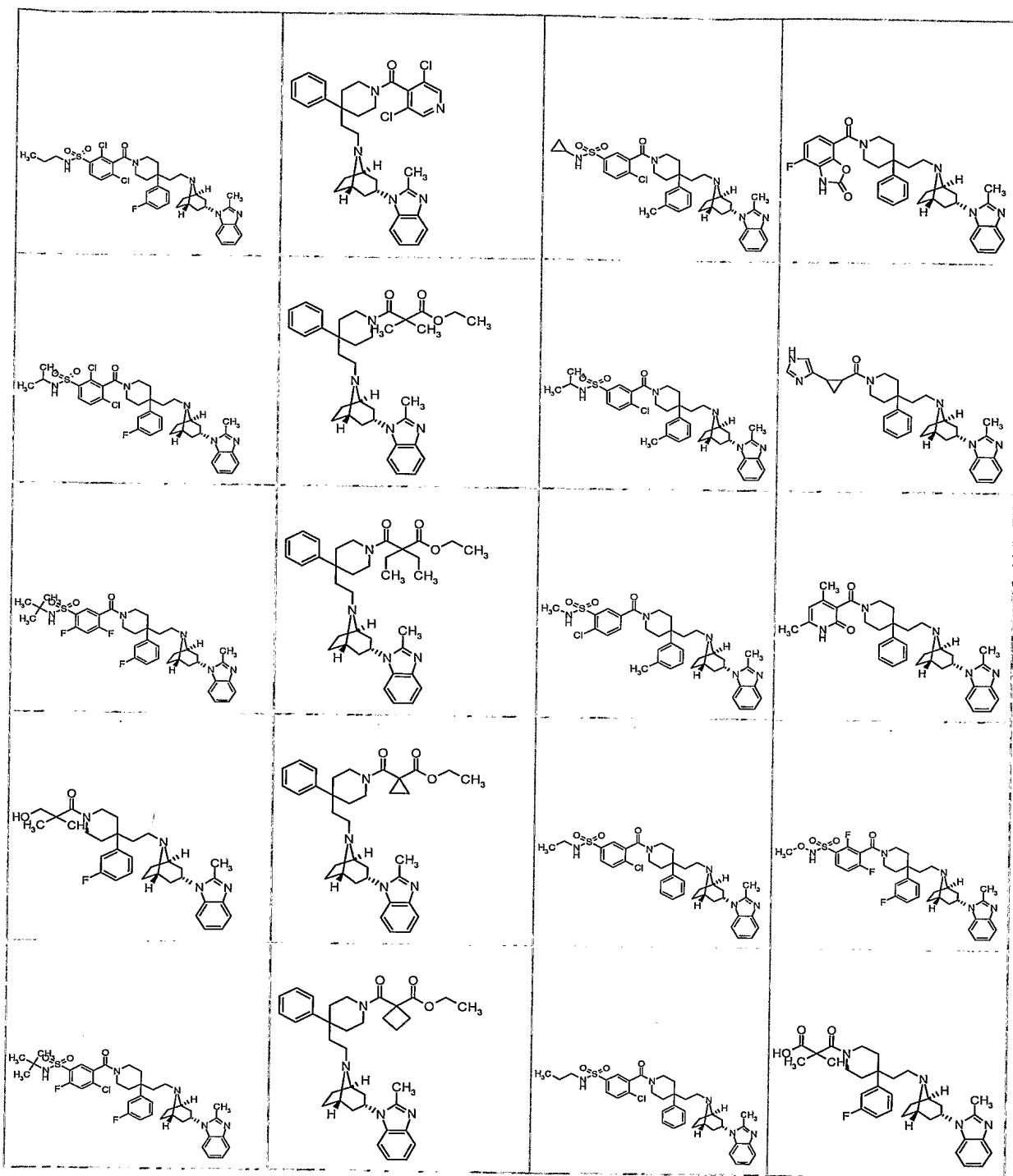


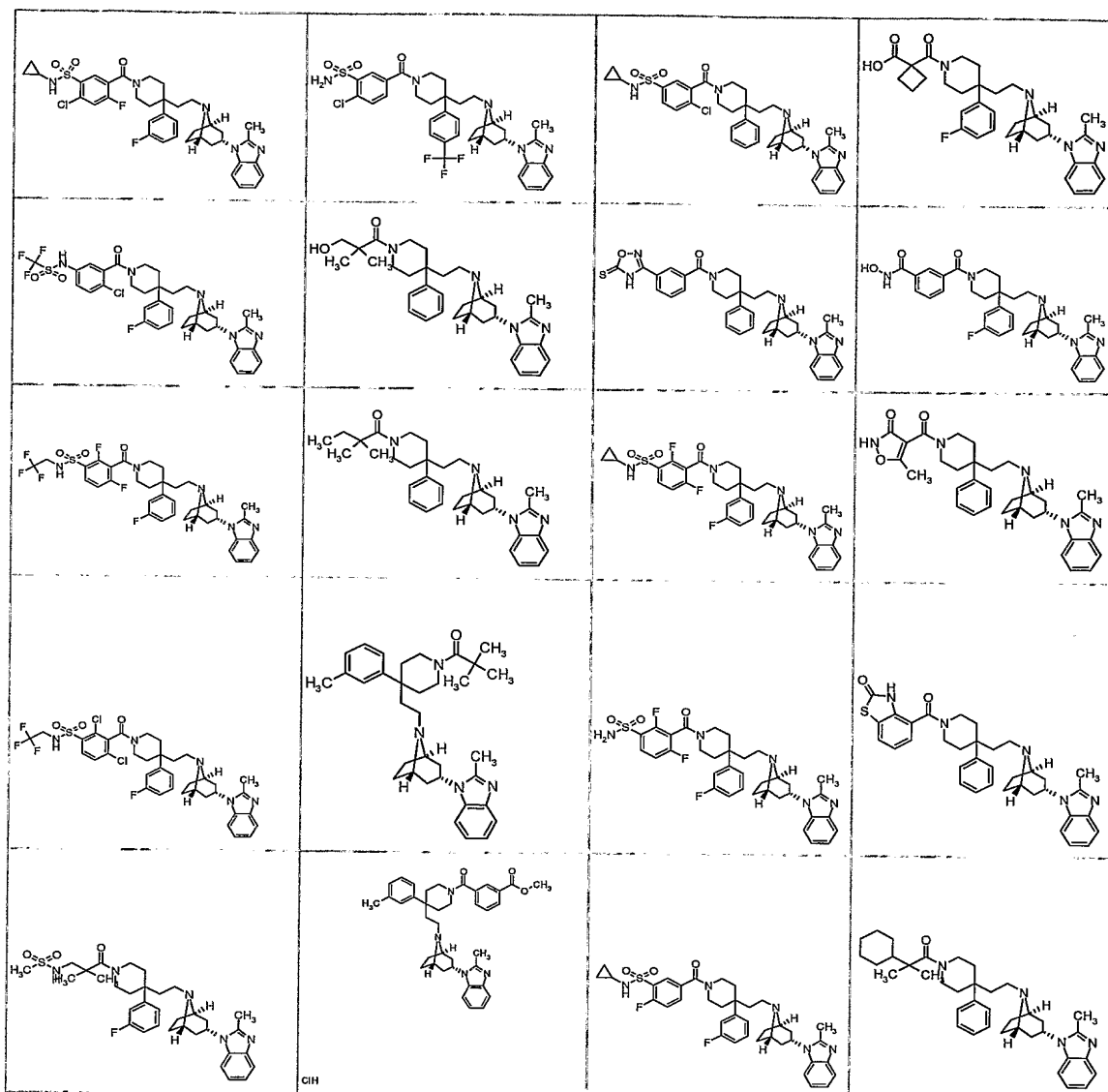




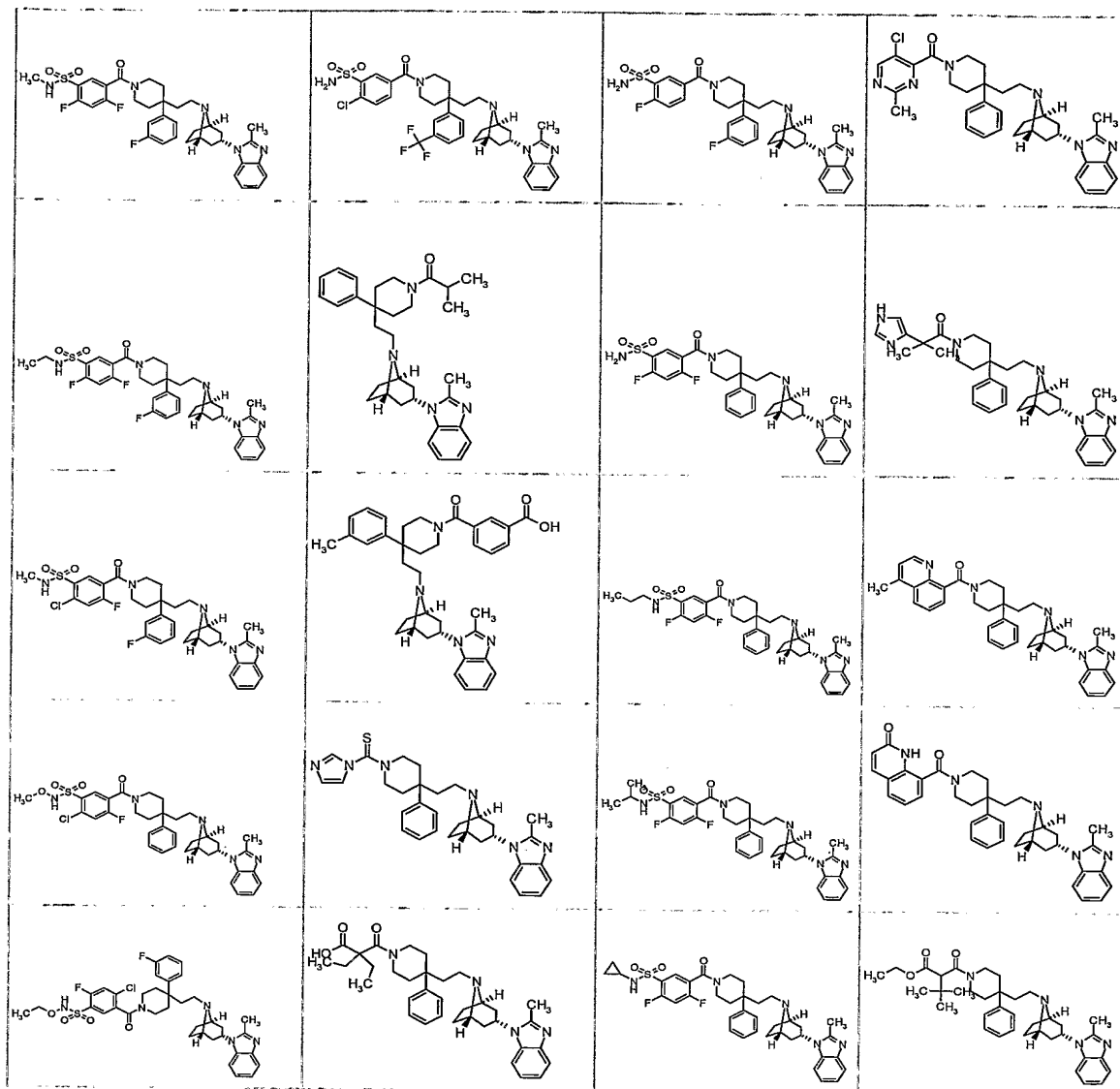


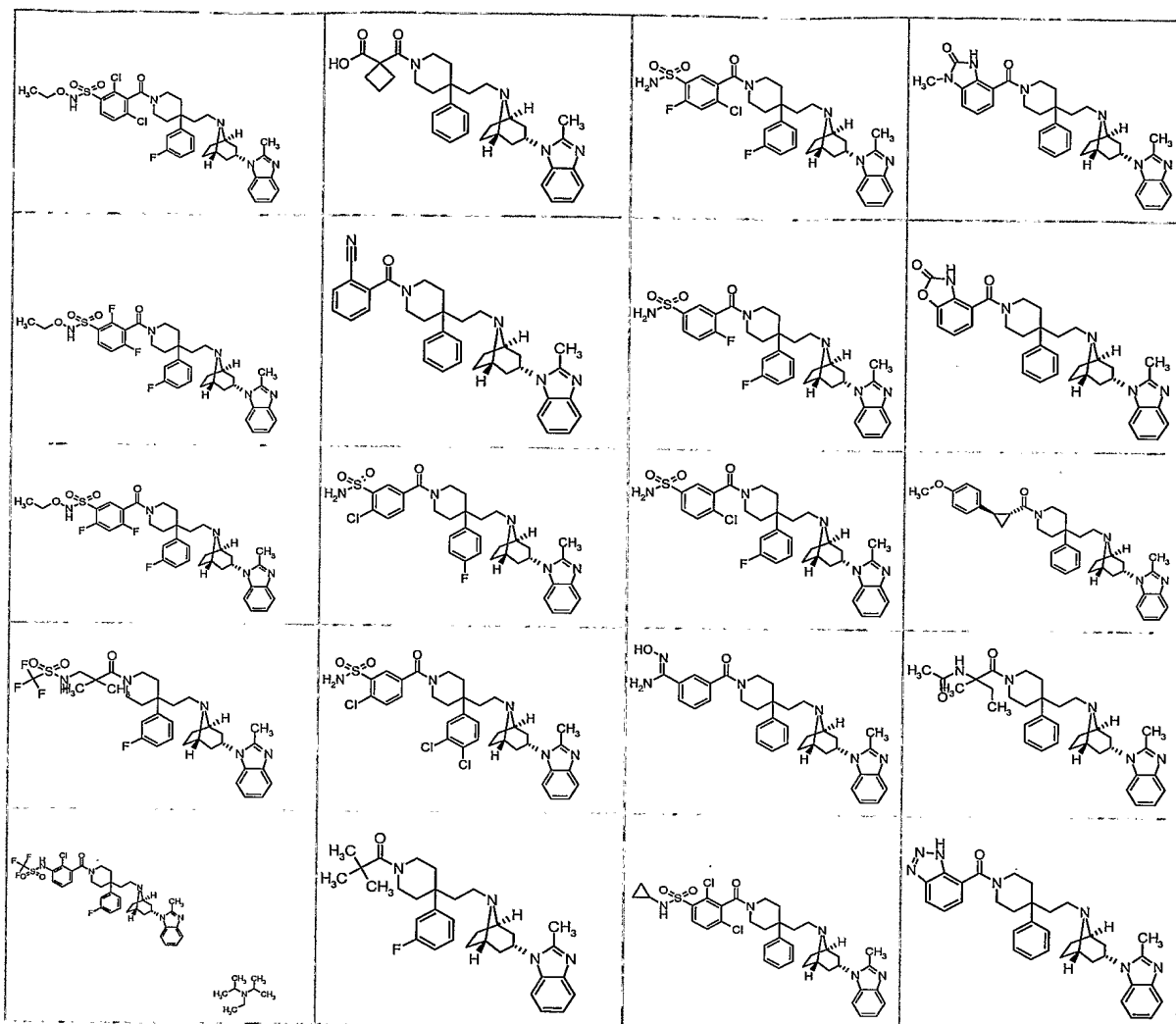


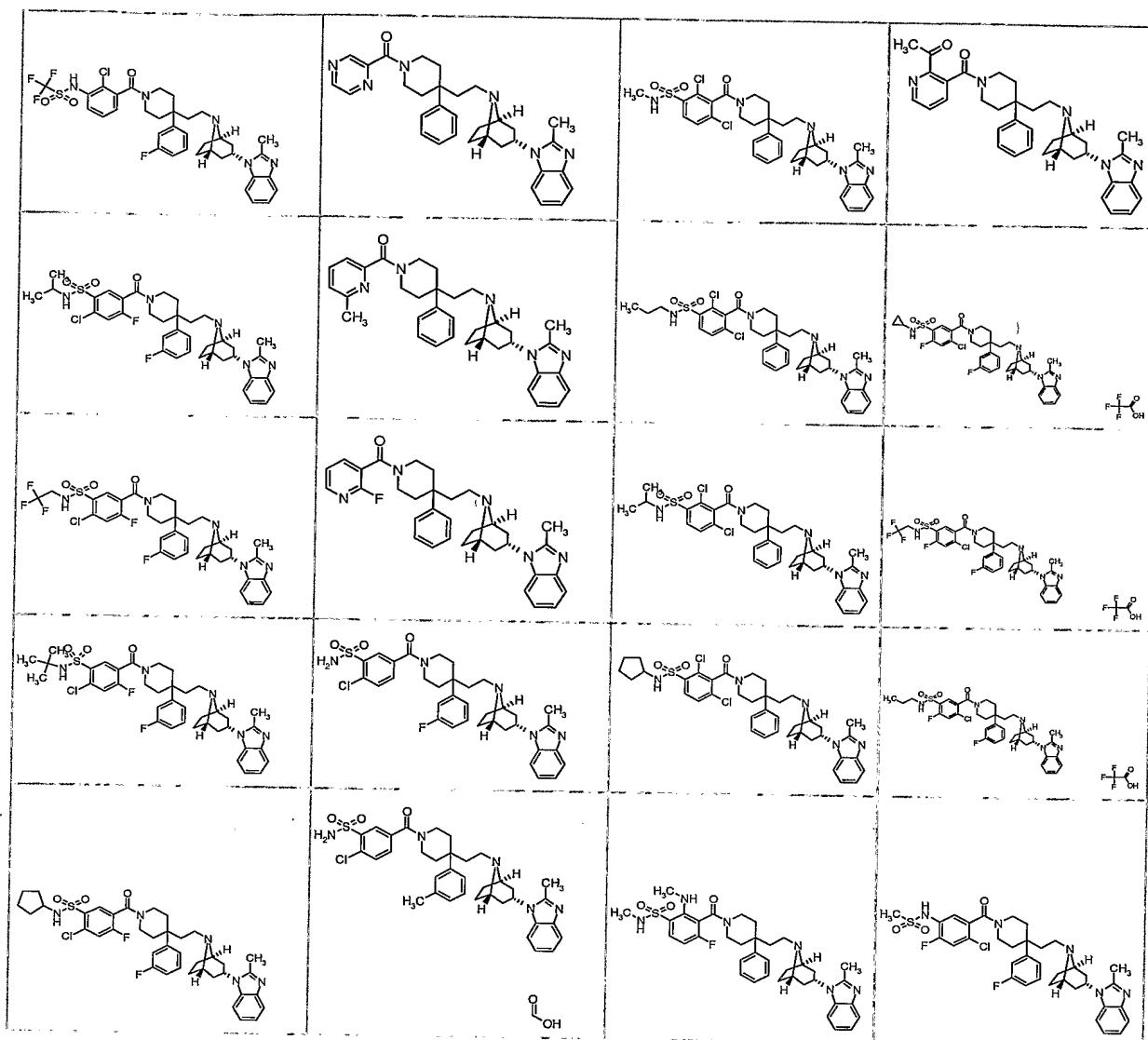


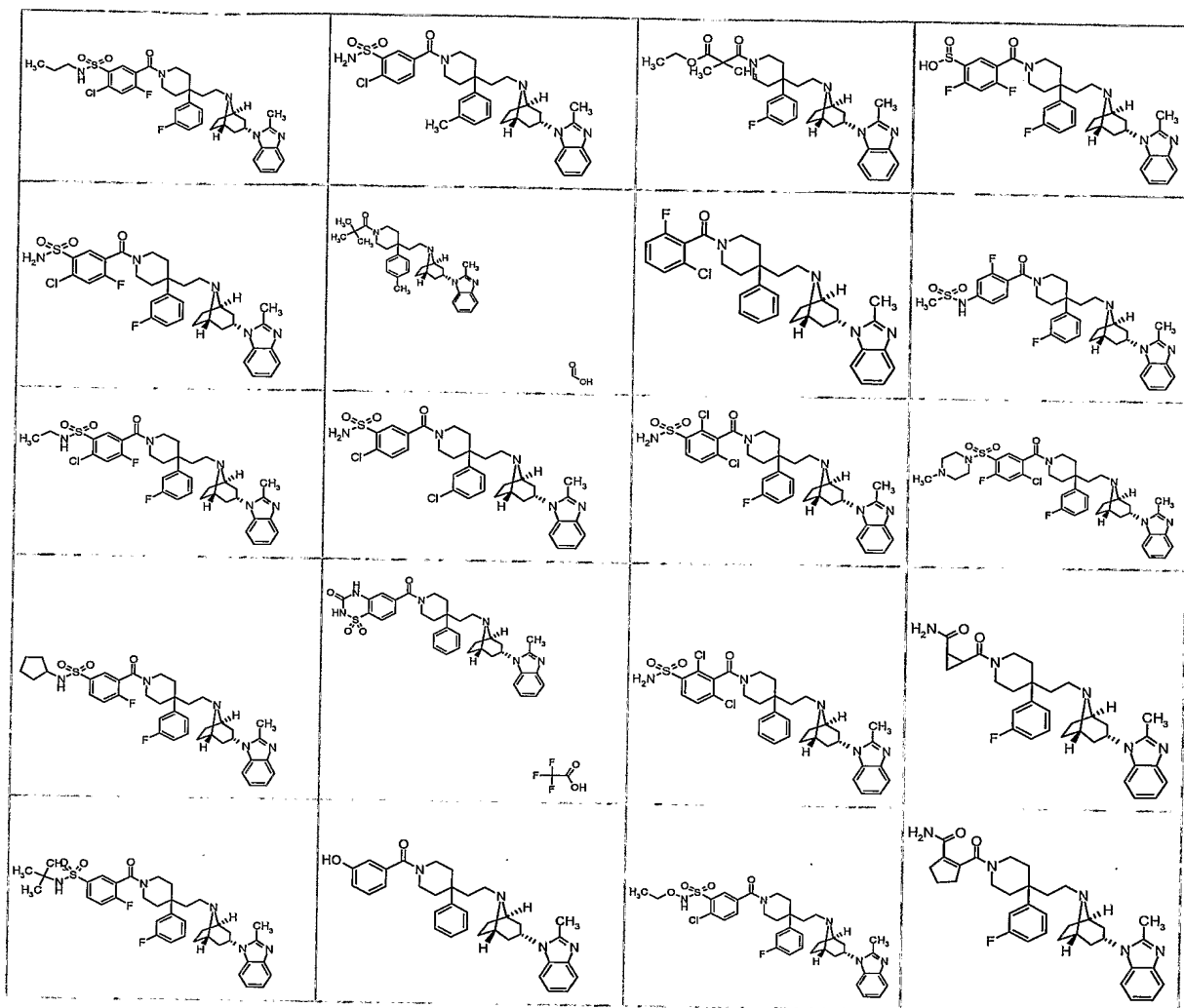


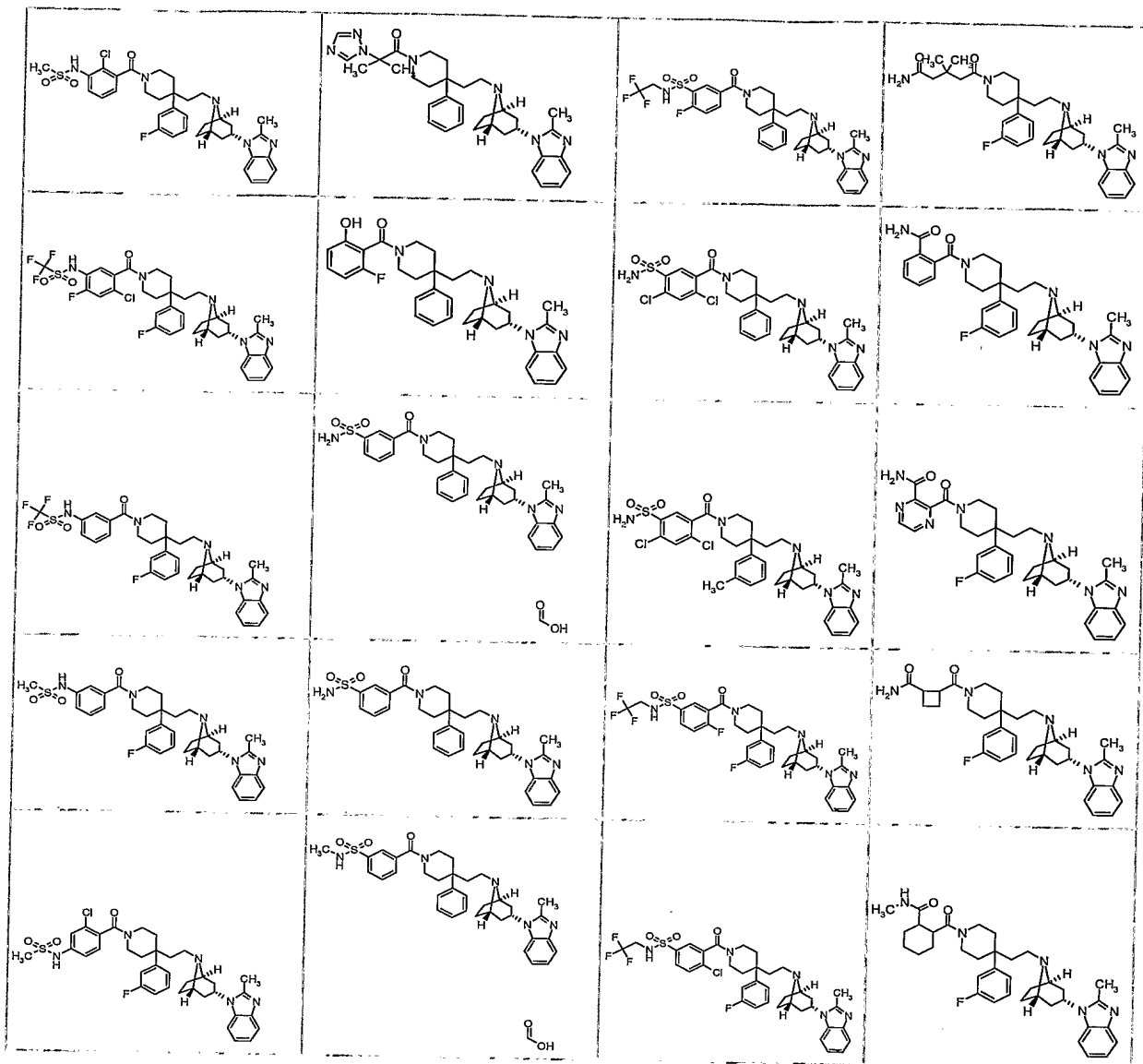
ClH

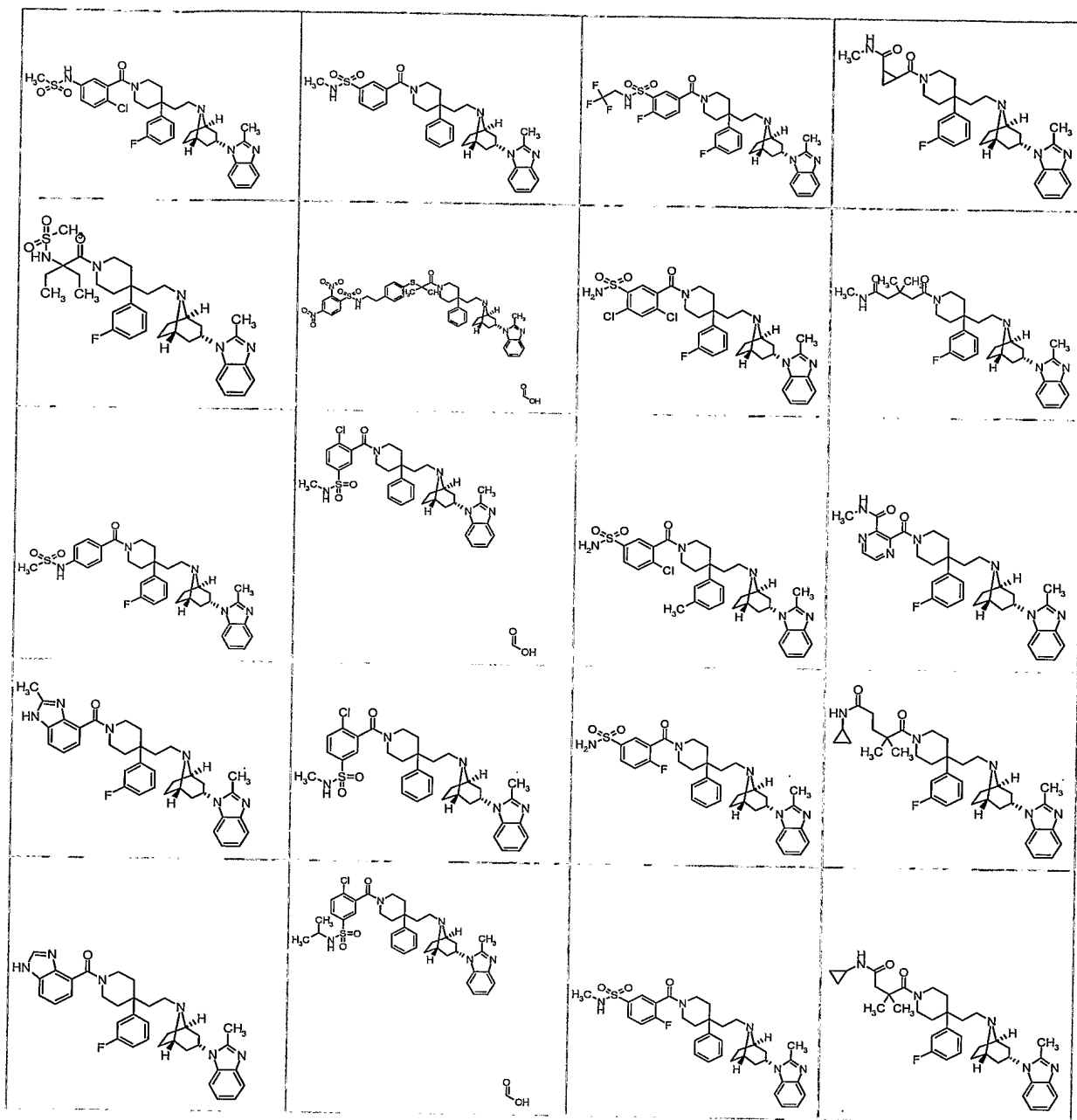


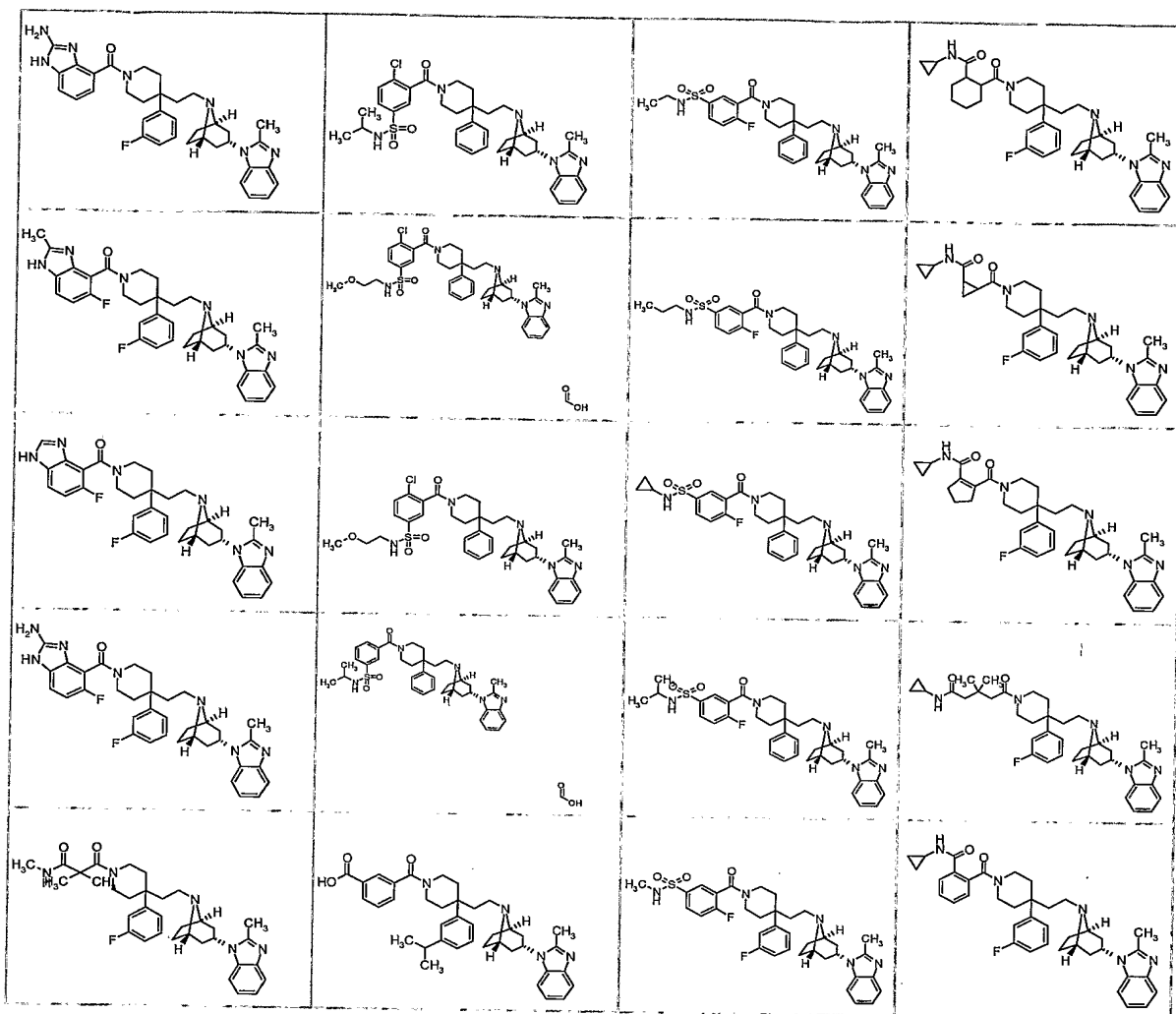


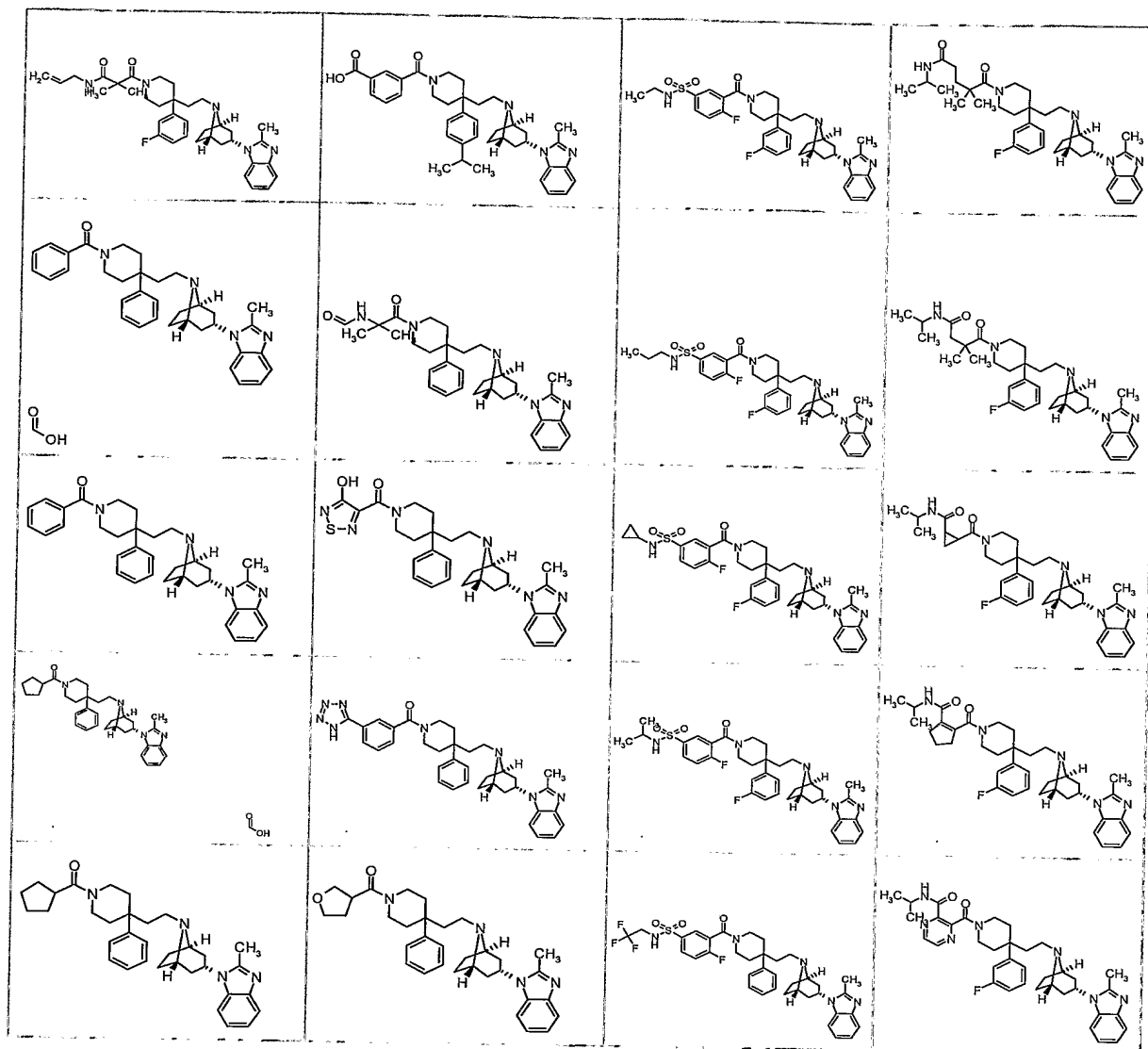


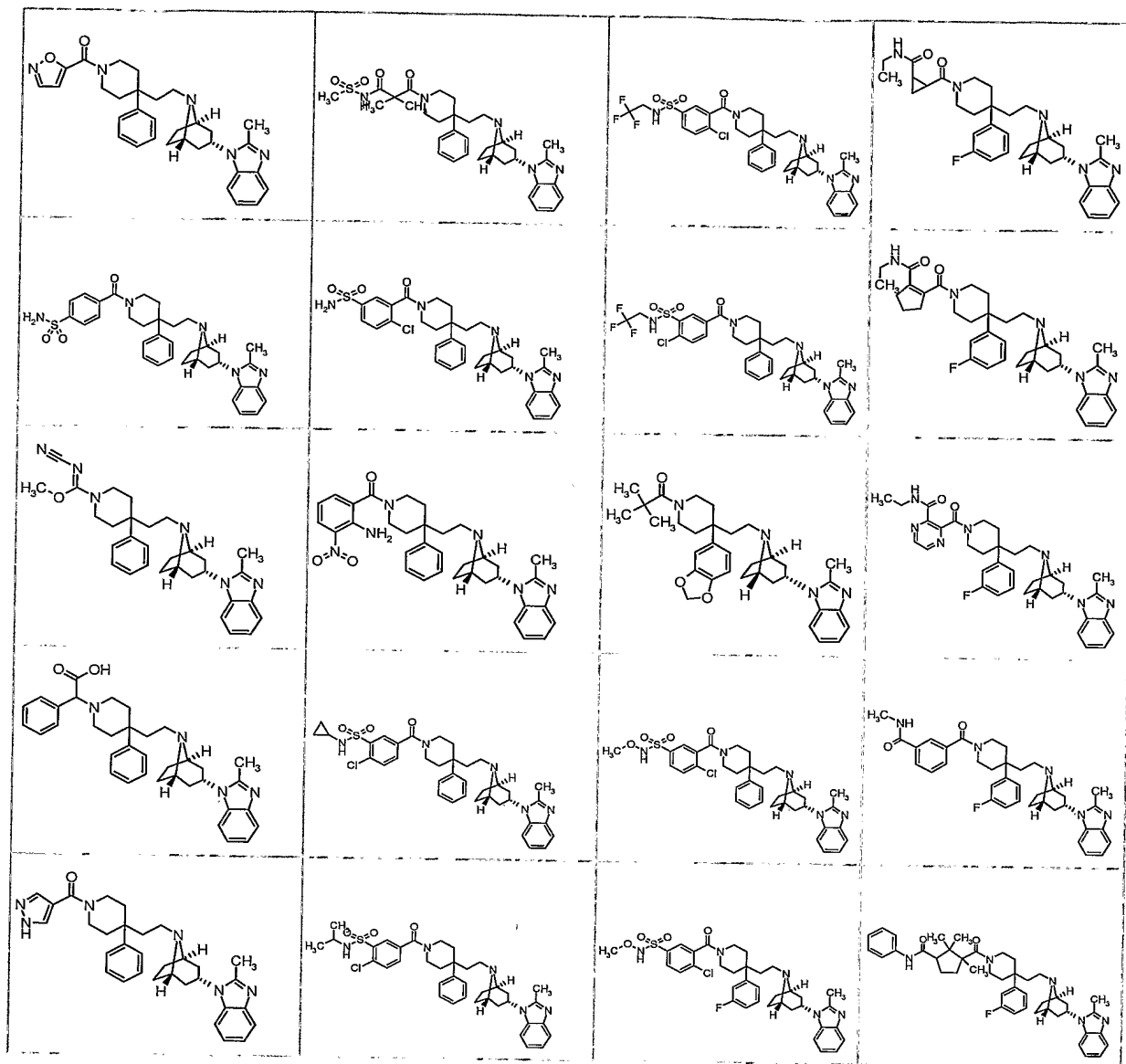


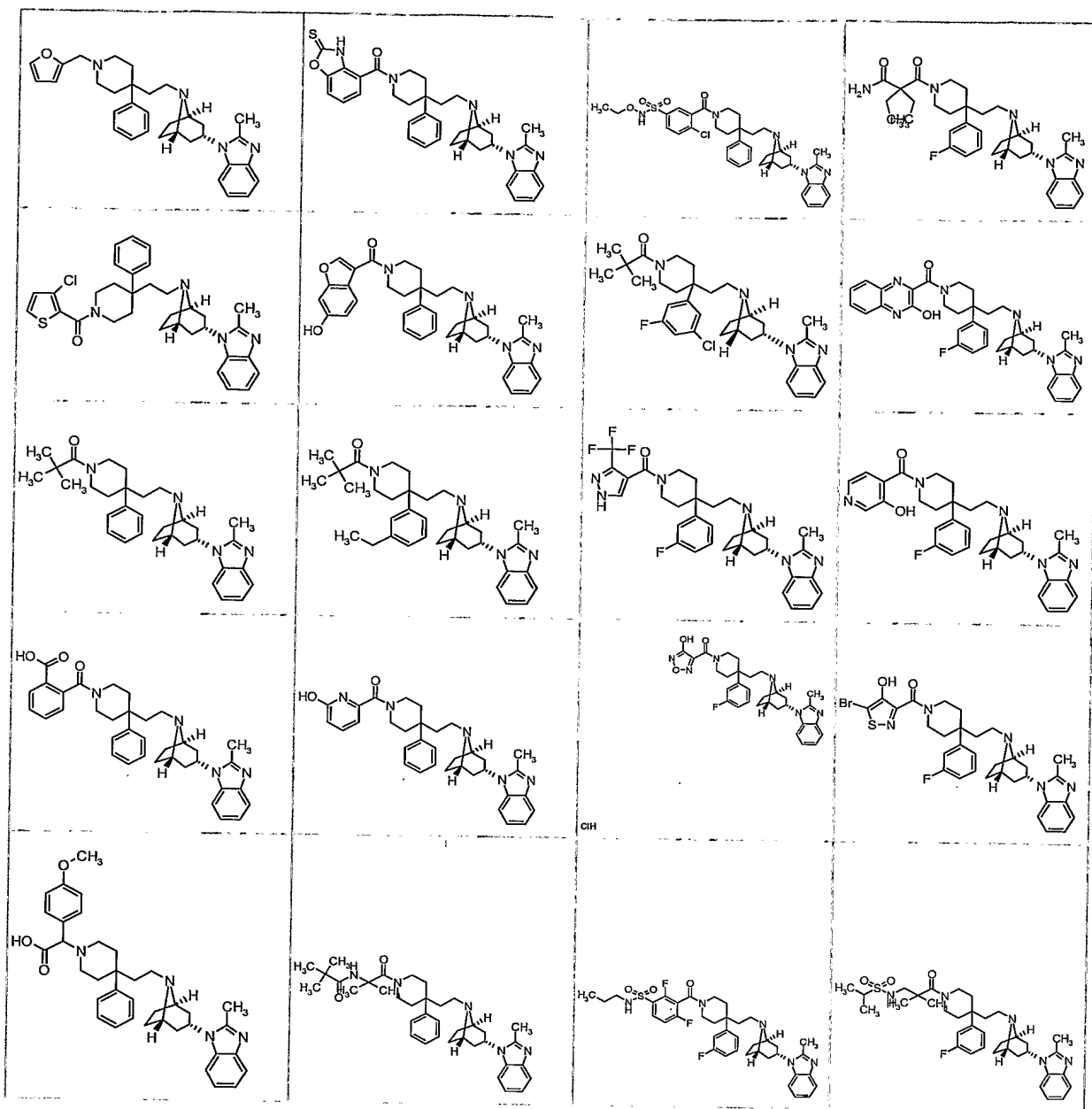


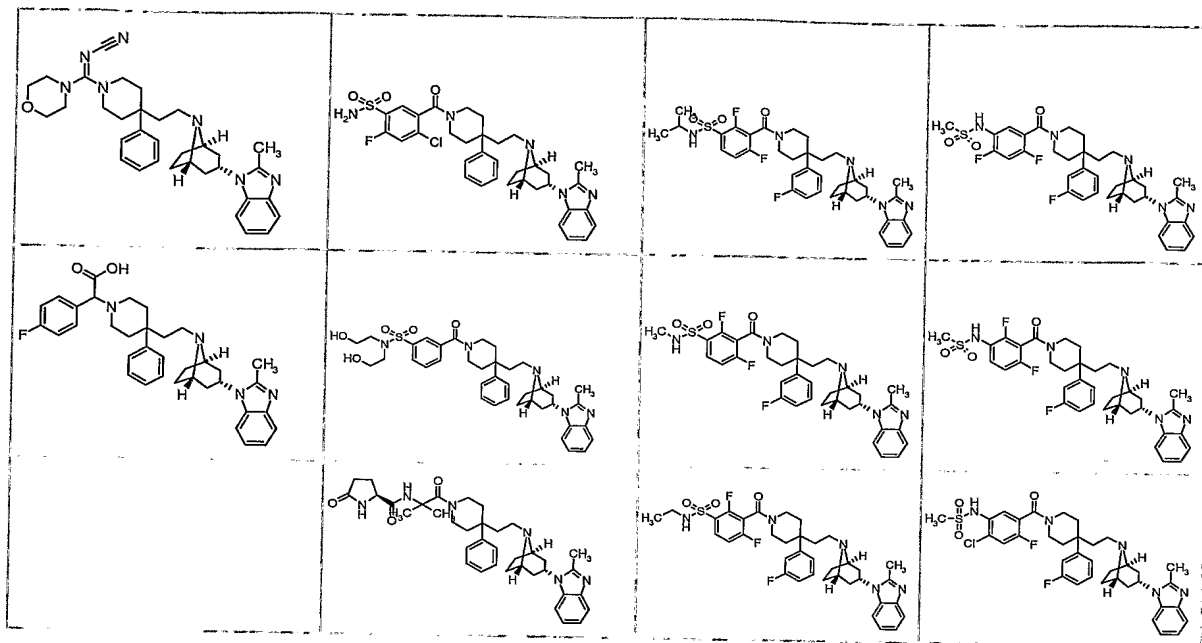












25. A composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.
26. The composition according to claim 25 further comprising a second therapeutic agent.
27. The composition according to claim 25 in the form of a tablet or capsule.
28. The composition according to claim 25 in the form of a liquid.
29. The composition according to claim 26, wherein said second therapeutic agent is chosen from (1- α , 2- β , 3- α)-9-[2,3-bis(hydroxy methyl)cyclobutyl]guanine [(-)BHCG, SQ-34514, lobucavir], 9-[(2R,3R,4S)-3,4-bis(hydroxy methyl)-2-oxetanosyl]adenine (oxetanocin-G), acyclic nucleosides, ribonucleotide reductase inhibitors, nucleoside reverse transcriptase inhibitors, protease inhibitors, interferons, renal excretion inhibitors, nucleoside transport inhibitors, immunomodulators, non-nucleoside reverse transcriptase inhibitors, glycoprotein 120 antagonists, cytokine antagonists, integrase inhibitors, and fusion inhibitors.
30. The composition according to claim 29, wherein said acyclic nucleoside is chosen from acyclovir, valaciclovir, famciclovir, ganciclovir, penciclovir, acyclic nucleoside phosphonates, (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC), [[[2-(6-amino-9H-purin-9-yl)ethoxy]methyl]phosphinylidene]bis(oxymethylene)-2,2-dimethylpropanoic acid (bis-POM PMEA, adefovir dipivoxil), [[[1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid (tenofovir) and (R)-[[2-(6-Amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid bis-(isopropoxycarbonyloxymethyl)ester (bis-POC-PPMA).
31. The composition according to claim 29, wherein said ribonucleotide reductase inhibitor is chosen from 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl]thiocarbonohydrazone and hydroxyurea.

32. The composition according to claim 29, wherein said nucleoside reverse transcriptase inhibitor is chosen from 3'-azido-3'-deoxythymidine (AZT, zidovudine), 2',3'-dideoxycytidine (ddC, zalcitabine), 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine (ddI, didanosine), 2',3'-didehydrothymidine (d4T, stavudine), (-)-beta-D-2,6-diamino purine dioxolane (DAPD), 3'-azido-2',3'-dideoxy thymidine-5'-H-phosphonate (phosphonovir), 2'-deoxy-5-iodo-uridine (idoxuridine), (-)-cis-1-(2-hydroxy methyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine), cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol (abacavir), 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), and ABT-606 (2HM-H2G) ribavirin.

33. The composition according to claim 29, wherein said protease inhibitor is chosen from indinavir, ritonavir, nelfinavir, amprenavir, saquinavir, fosamprenavir, (R)-N-tert-butyl-3-[(2S,3S)-2-hydroxy-3-N-[(R)-2-N-(isoquinolin-5-yloxyacetyl) amino-3-methylthiopropionoyl]amino-4-phenylbutanoyl]-5,5-dimethyl-1,3-thiazolidine-4-carboxamide (KNI-272), 4R-(4alpha,5alpha,6beta)]-1,3-bis[(3-aminophenyl) methyl]hexahydro-5,6-dihydroxy-4,7-bis(phenylmethyl)-2H-1,3-diazepin-2-one dimethanesulfonate (mozenavir), 3-[1-[3-[2-(5-trifluoromethylpyridinyl)-sulfonylamino] phenyl]propyl]-4-hydroxy-6alpha-phenethyl-6beta-propyl-5,6-dihydro-2-pyranone (tipranavir), N'-[2(S)-Hydroxy-3(S)-[N-(methoxycarbonyl)-l-tert-leucylamino]-4- phenylbutyl-N^{alpha}-(methoxycarbonyl)-N'-[4-(2-pyridyl)benzyl]-L-tert-leucylhydrazide (BMS-232632), 3-(2(S)-Hydroxy-3(S)-(3-hydroxy-2-methylbenzamido)-4-phenylbutanoyl)-5,5-dimethyl-N-(2-methylbenzyl) thiazolidine-4(R)-carboxamide (AG-1776), and N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(1-(4-benzo[b]furanylmethyl)-2(S)-N'-(tert-butylcarboxamido)piperazinyl)pentanamide (MK-944A).

34. The composition according to claim 29, wherein said interferon is α -interferon.
35. The composition according to claim 29, wherein said renal excretion inhibitor is probenecid.
36. The composition according to claim 29, wherein said nucleoside transport inhibitor is chosen from dipyridamole, pentoxifylline, N-acetylcysteine (NAC), Procysteine, α -trichosanthin and phosphono-formic acid.
37. The composition according to claim 29, wherein said immunomodulator is chosen from interleukin II, thymosin, granulocyte macrophage colony stimulating factors, erythropoietin, soluble CD₄ and genetically engineered derivatives thereto.
38. The composition according to claim 29, wherein said non-nucleoside reverse transcriptase inhibitor (NNRTI) is chosen from nevirapine (BI-RG-587), α -((2-acetyl-5-methyl phenyl)amino)-2,6-dichloro-benzeneacetamide (loviride), 1-[3-(isopropyl amino)-2-pyridyl]-4-[5-(methane-sulfonamido)-1H-indol-2-ylcarbonyl]piperazine monomethanesulfonate (delavirdine), (10R, 11S, 12S)-12-hydroxy-6, 6, 10, 11-tetramethyl-4-propyl-11,12-dihydro-2H, 6H, 10H-benzo(1, 2-b:3, 4-b':5, 6-b'')tripyrans-2-one ((+) calanolide A), (4S)-6-chloro-4-[1E]-cyclopropylethenyl)-3,4-dihydro-4-(trifluoro-methyl)-2(1H)-quinazolinone (DPC-083), (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one (efavirenz, DMP 266), 1-(ethoxymethyl)-5-(1-methylethyl)-6-(phenylmethyl)-2,4(1H,3H)-pyrimidinedione (MKC-442), and 5-(3,5-dichlorophenyl)thio-4-isopropyl-1-(4-pyridyl)methyl-1H-imidazol-2-ylmethyl carbamate (capravirine).
39. The composition according to claim 29, wherein said glycoprotein 120 antagonist is chosen from PRO-2000, PRO-542, and 1,4-bis[3-[(2,4-

dichlorophenyl) carbonylamino]-2-oxo-5,8-disodiumsulfanyl]naphthalyl-2, 5-dimethoxyphenyl-1,4-dihydrazone (FP-21399).

40. The composition according to claim 29, wherein said cytokine antagonists is chosen from reticulose (Product-R), 1,1'-azobis-formamide (ADA), and 1,11-(1,4-phenylene bis(methylene))bis-1,4,8,11-tetraaza cyclotetradecane octahydrochloride (AMD-3100).

41. The composition according to claim 33, wherein said protease inhibitor is ritonavir.

42. A method of antagonizing a chemokine CCR-5 receptor activity in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a composition according to claim 25.

43. A method of antagonizing a chemokine CCR-5 receptor activity in a biological sample, comprising contacting the biological sample with an effective amount of a compound according to Claim 1 or a composition according to claim 25.

44. A method of treating a viral infection in a patient comprising administering to said patient a therapeutically effective amount of a composition according to claim 25.

45. The method according to claim 44 wherein the viral infection is an HIV infection.

46. A method of treating of a viral infection in a patient comprising administering to said patient a therapeutically effective amount of a composition according to Claim 26.

47. The method according to claim 33 wherein the viral infection is an HIV infection.

48. A method of treating a disease or disorder selected from AIDS related complex, progressive generalized lymphadenopathy, Kaposi's sarcoma,

thrombocytopenic purpura, AIDS-related neurological conditions, multiple sclerosis, tropical paraperesis, anti-HIV antibody-positive, or HIV-positive conditions in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a composition according to claim 25.

49. The method according to claim 48, wherein said disease or disorder is AIDS related complex, Kaposi's sarcoma or AIDS dementia.

50. A method of treating a disease or disorder selected from AIDS related complex, progressive generalized lymphadenopathy, Kaposi's sarcoma, thrombocytopenic purpura, AIDS-related neurological conditions, multiple sclerosis, tropical paraperesis, anti-HIV antibody-positive, or HIV-positive conditions in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a composition according Claim 26.

51. The method according to claim 50, wherein said disease or disorder is AIDS related complex, Kaposi's sarcoma or AID dementia.

52. A method of treating or preventing multiple sclerosis, rheumatoid arthritis, autoimmune diabetes, chronic implant rejection, asthma, rheumatoid arthritis, Crohns Disease, inflammatory bowel disease, chronic inflammatory disease, glomerular disease, nephrotoxic serum nephritis, kidney disease, Alzheimer's Disease, autoimmune encephalomyelitis, arterial thrombosis, allergic rhinitis, arteriosclerosis, Sjogren's syndrome, systemic lupus erythematosus, graft rejection, cancers with leukocyte infiltration of the skin or organs, human papilloma virus infection, prostate cancer, wound healing, amyotrophic lateral sclerosis, immune-mediated disorders, or bacterial infections in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a composition according to claim 25.

53. A method of treating or preventing multiple sclerosis, rheumatoid arthritis, autoimmune diabetes, chronic implant rejection, asthma, rheumatoid arthritis, Crohns Disease, inflammatory bowel disease, chronic inflammatory disease, glomerular disease, nephrotoxic serum nephritis, kidney disease, Alzheimer's Disease, autoimmune encephalomyelitis, arterial thrombosis, allergic rhinitis, arteriosclerosis, Sjogren's syndrome (dermatomyositis), systemic lupus erythematosus, graft rejection, cancers with leukocyte infiltration of the skin or organs, human papilloma virus infection, prostate cancer, wound healing, amyotrophic lateral sclerosis or immune-mediated disorders in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a composition according to Claim 26.

54. A compound according to any one of claims 1-24 for use in medical therapy.

55. Use of a compound according to any one of claims 1-24 in the manufacture of a medicament for the treatment of a viral infection.

56. The use according to claim 55 wherein the viral infection is an HIV infection.

57. Use of a compound according to any one of claims 1-24 in the manufacture of a medicament for the treatment or prophylaxis of a disease or disorder selected from AIDS related complex, progressive generalized lymphadenopathy, Kaposi's sarcoma, thrombocytopenic purpura, AIDS-related neurological conditions, multiple sclerosis, tropical paraperesis, anti-HIV antibody-positive, and HIV-positive conditions.

58. The use according to claim 57 wherein said disease or disorder is AIDS related complex, Kaposi's sarcoma or AID dementia.

59. A use of a compound according to any one of claims 1-24 in the manufacture of a medicament for the treatment of multiple sclerosis,

rheumatoid arthritis, autoimmune diabetes, chronic implant rejection, asthma, rheumatoid arthritis, Crohns Disease, inflammatory bowel disease, chronic inflammatory disease, glomerular disease, nephrotoxic serum nephritis, kidney disease, Alzheimer's Disease, autoimmune encephalomyelitis, arterial thrombosis, allergic rhinitis, arteriosclerosis, Sjogren's syndrome, systemic lupus erythematosus, graft rejection, cancers with leukocyte infiltration of the skin or organs, human papilloma virus infection, prostate cancer, wound healing, amyotrophic lateral sclerosis or immune-mediated disorders.

60. The use according to any one of claims 55-59, said medicament further comprises a second therapeutic agent.

61. The use according to claim 60 wherein said second therapeutic agent is chosen from (1-alpha, 2-beta, 3-alpha)-9-[2,3-bis(hydroxy methyl)cyclobutyl] guanine [(-)BHCG, SQ-34514, lobucavir], 9-[(2R,3R,4S)-3,4-bis(hydroxy methyl)-2-oxetanosyl]adenine (oxetanocin-G), acyclic nucleosides, ribonucleotide reductase inhibitors, nucleoside reverse transcriptase inhibitors, protease inhibitors, interferons, renal excretion inhibitors, nucleoside transport inhibitors, immunomodulators, non-nucleoside reverse transcriptase inhibitors, glycoprotein 120 antagonists, cytokine antagonists, integrase inhibitors, and fusion inhibitors.